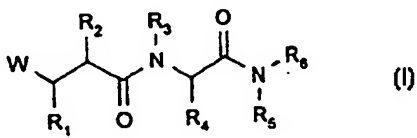
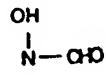
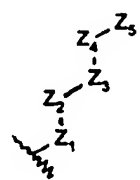




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 277/46, A61K 31/425, C07D 213/75, A61K 31/44, C07D 285/12, 239/42, 417/12</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/38179 (43) International Publication Date: 3 September 1998 (03.09.98)</p>
<p>(21) International Application Number: PCT/EP98/01015 (22) International Filing Date: 24 February 1998 (24.02.98) (30) Priority Data: 60/039,112 26 February 1997 (26.02.97) US (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): ANDREWS, Robert, Carl [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). ANDERSEN, Marc, Werner [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). STANFORD, Jennifer, Badiang [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). BUBACZ, Dulcie, Garrido [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). CHAN, Joseph, Howing [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). COWAN, David, John [US/US]; 5121 Copper Ridge Drive #207, Durham, NC 27707 (US). GAUL, Michael, David</p>		<p>[US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). McDOUGALD, Darryl, Lynn [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). MUSSO, David, Lee [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). RABINOWITZ, Michael, Howard [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). WIETHE, Robert, William [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). (74) Agent: REED, Michael, A.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: REVERSE HYDROXAMATE DERIVATIVES AS METALLOPROTEASE INHIBITORS</p> <div style="text-align: center;">  <p>(I)</p> </div> <div style="display: flex; justify-content: space-around; align-items: flex-end;"> <div style="text-align: center;">  <p>(a)</p> </div> <div style="text-align: center;">  <p>(b)</p> </div> </div>		
<p>(57) Abstract</p> <p>A family of compounds having general structural formula (I) wherein W is a reverse hydroxamic acid group (a); R₅ is hydrogen or lower alkyl; R₆ is (b); where Z₁ is heteroarylene; preferably: R₁ is methyl, ethyl, isopropyl, n-propyl or 3,3,3-trifluoro-n-propyl; R₂ is isobutyl or sec-butyl; R₃ is hydrogen; R₄ is tert-butyl, sec-butyl, 1-methoxy-1-ethyl or 2-(2-pyridylcarbonylamino)-1-ethyl; R₅ is hydrogen; and R₆ is 2-thiazolyl or 2-pyridyl. Such compounds show potent inhibition of MMP's, cell-free TNF convertase enzyme and TNF release from cells, and in some cases inhibit TNF convertase and TNF release from cells in preference to matrix metalloproteases.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China			PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

REVERSE HYDROXAMATE DERIVATIVES AS METALLOPROTEASE INHIBITORS

5 FIELD OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds generally pharmacologically useful as agents in those disease states alleviated by the inhibition or antagonism of matrix metalloproteases, metalloproteases, and/or tumor necrosis
10 factor-alpha (TNF), which pathologically involve aberrant extracellular matrix degradation, shedding of cell surface protein ectodomains, and/or TNF synthesis, such disease states including arthritis, tumor metastasis and diabetes. The aforementioned pharmacologic activities are useful in the treatment of mammals.

More specifically, the compounds of the present invention can be used in the
15 treatment of rheumatoid arthritis, osteoarthritis, inflammatory bowel syndromes, periodontal disease, aberrant angiogenesis, tumor invasion and metastasis, corneal ulceration and the complications of diabetes. At the present time, there is a need in the areas of rheumatology, oncology, dentistry, ophthalmology, gastroenterology, cardiology, neurology, nephrology, infectious disease and endocrinology therapy for
20 such agents.

BACKGROUND OF THE INVENTION

The matrix metalloprotease (MMP) family of zinc endoproteases includes fibroblast collagenase (MMP-1, collagenase-1), neutrophil collagenase (MMP-8, collagenase-2), chondrocyte collagenase (MMP-13, collagenase-3), gelatinases A and B (MMP's 2 and 9), and members of the stromelysin family such as stromelysin-1 (MMP-3), stromelysin-3 (MMP-11), and matrilysin (MMP-7). These enzymes accelerate breakdown of connective tissue by catalyzed resorption of the extracellular matrix. This is a feature of diverse pathologies; therefore, inhibitors of one or more
25 of the matrix metalloproteases would have utility in a wide range of disease states such as in abrogating the initiation of tumor metastasis and angiogenesis and in halting the pathogenesis of demyelinating diseases of the nervous system, multiple sclerosis being one example. MMP inhibitors would also find utility in diseases involving connective tissue degradation in the joint, as occurs in osteoarthritis and
30 rheumatoid arthritis. MMP's-1 and -3 have been found in elevated levels in the synovial fluid of patients with rheumatoid arthritis and osteoarthritis.

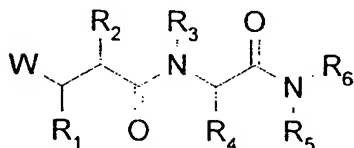
Collagenase-3 (MMP-13) is a member of the family of MMP's which preferentially digest collagen. Collagenase-3 is one of the more newly characterized MMP's; biochemical studies on the recombinant protein have demonstrated that it cleaves type II collagen, the predominant matrix component of articular cartilage, more efficiently than either MMP-1 or MMP-2 and that it is expressed by chondrocytes in osteoarthritic cartilage. These data would implicate collagenase-3 as a significant target in rheumatoid arthritis and osteoarthritis for inhibition by MMP inhibitors.

Compounds which inhibit the activities of one or more of the matrix metalloproteases are recognized as having therapeutic benefit in one or more pathologies where MMP activity is upregulated, such as:

- i) inflammatory/autoimmune diseases, which include rheumatoid arthritis, osteoarthritis, Crohn's disease and other inflammatory bowel diseases, periodontal disease, gingivitis, and corneal ulceration;
- ii) cardiovascular diseases, which include atherosclerosis and restenosis;
- vi) metabolic diseases, which includes complications of diabetes, osteoporosis, and other disorders involving resorption of bone;
- iii) neurologic diseases, such as multiple sclerosis and other demyelination ailments;
- iv) diseases of cancer and malignancy, including colorectal cancer and leukemias, tumor invasion, and metastatic and angiogenic events thereof;
- v) renal diseases, including nephrotic syndromes and glomerulonephritis; and
- vi) infectious diseases, including those mediated by viruses, bacteria, and fungi.

Many inhibitors of matrix metalloproteases have been disclosed, including some structure activity relationships for a series of carboxylalkylamine inhibitors. These molecules are exemplary for MMP inhibitors in general. They generally embody a functional group capable of tightly binding the zinc cofactor at the enzyme active site, which is contained within a peptidic or pseudopeptide structure. Zinc binding groups among the MMP inhibitor art have included hydroxamic acid, reverse hydroxamic acid, thiol, carboxylate, and phosphinate.

Hydroxamate metalloprotease inhibitors disclosed in the art usually have the following general structure (I):



(I)

where W is a zinc-chelating acyl derivative group of the formula $-C(O)NHOH$ (which by convention and in this application are referred to as "forward hydroxamates") or a zinc-chelating substituted amine group of the formula $-NH(OH)C(O)R$ (which by convention and in this application are referred to as "reverse hydroxamates"), where R is usually hydrogen or alkyl. The other substituents vary according to specifications expressed by the art disclosure. It is understood and demonstrated that variations in these substituents can have dramatic effects on potency and selectivities between the matrix metalloproteases.

Suppression of MMP activity in conditions characterized by its overproduction would be of benefit, and compounds which inhibit MMP's would act in this manner at a specific target and be useful and of benefit.

Accordingly it is an object of the present invention to provide a potent, specific, orally active inhibitor of MMP's.

Tumor necrosis factor- α (TNF α), hereinafter called "TNF", is a mammalian protein capable of inducing cellular effects by virtue of its interaction with specific cellular receptors. It is initially characterized and so named due to its ability to cause death of cancerous cells. It is produced primarily by activated monocytes and macrophages. Human TNF is produced as a larger pro-form of 26 kD which is processed to a secreted 17 kD mature form by proteolytic processing of the alanine-76 - valine-77 peptide bond.

Recently, certain compounds having matrix metalloprotease - inhibiting activity have been found to inhibit the release of mature 17 kD TNF from cells. Further, these inhibitors also protect mice from a lethal dose of endotoxin indicating that the compounds can inhibit TNF secretion in vivo. These compounds inhibit the cell-associated proteolytic processing of the 26 kD pro-TNF to the mature 17 kD form. The proteolytic activity is thought to reside in an intracellular or cell-associated specific enzyme or family of enzymes, which by convention is called a "TNF convertase", distinct from the matrix metalloproteases but related in that both contain a zinc cation at the active site. TNF convertase enzymatic activity can be detected in monocyte membrane fractions, and the enzyme activity can be inhibited by certain matrix metalloprotease - inhibiting compounds.

Metalloprotease - like activity is also thought to contribute to the shedding of certain cell surface protein ectodomains such as L-selectin, fibronectin, thyrotropin stimulating hormone receptor, transforming growth factor alpha precursor, low density lipoprotein receptor, beta amyloid precursor protein, interleukin-6 receptor alpha subunit, Fas ligand, CD40 ligand, epidermal growth factor receptor,

macrophage colony stimulating factor, interleukin-1 receptor type II, CD30, and tumor necrosis factor receptors type I and II.

TNF is known to mediate many biological responses in vivo. Preclinical and clinical studies in animals and humans with specific TNF neutralizing antibodies, soluble TNF receptor constructs, and TNF detection techniques have implicated TNF as a mediator in numerous pathologies. The compounds of the present invention by virtue of their activity in inhibiting TNF production and/or their activity in preventing cell surface protein ectodomain shedding should show utility in the treatment of diverse pathologies such as:

- 5 i) inflammatory/autoimmune diseases, including but not limited to rheumatoid arthritis, osteoarthritis, Crohn's disease and other inflammatory bowel diseases and inflammatory gastrointestinal diseases, and systemic lupus erythematosus;
- 10 ii) reperfusion injuries, such as those caused by an initial ischemic event;
- 15 iii) systemic inflammatory response syndromes, including but not limited to sepsis, burn injury, pancreatitis, and adult respiratory distress syndrome;
- iv) allergic and dermatologic diseases, including but not limited to delayed type hypersensitivity, psoriasis, asthma, eczema, allergic rhinitis, and allergic conjunctivitis;
- 20 v) cardiovascular diseases, including but not limited to hyperlipidemia, myocardial infarction, atherosclerosis, and restenosis;
- vi) metabolic diseases, including but not limited to osteoporosis and diabetes;
- vii) neurologic diseases, including but not limited to Alzheimer's disease, Parkinson's disease, multiple sclerosis, aneurism, and stroke;
- 25 viii) transplant rejection, including but not limited to organ transplant rejection and graft versus host disease;
- ix) diseases of cancer and malignancy, including but not limited to colorectal cancer and leukemias;
- x) renal diseases, including but not limited to nephrotic syndromes and glomerulonephritis;
- 30 xi) cachexia and related wasting syndromes;
- xii) infectious diseases, including but not limited to HIV infection and neuropathy, Epstein-Barr viral infection, herpes viral infection, malaria, meningitis, leprosy, hepatitis (which includes hepatitis A, hepatitis B, and hepatitis C), infectious arthritis, leishmaniasis, Lyme disease, and viral encephalitis;
- 35 xiii) effects of disease therapy, including but not limited to cytokine therapy, chemotherapy, radiation therapy and therapies using anti-T-cell antibodies or cytotoxin-antibody conjugates; and

xiv) ocular diseases, including but not limited to macular degeneration.

Suppression of TNF activity in conditions characterized by its overproduction would be of benefit, and compounds which inhibit TNF convertase would act in this manner at a specific target and be useful and of benefit.

5 Accordingly it is another object of the present invention to provide a potent, specific, orally active inhibitor of TNF-alpha release from monocyte cells acting via inhibition of TNF-alpha converting enzyme (TNFc).

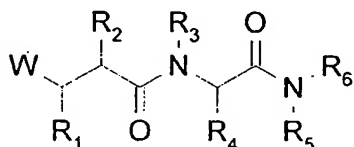
Suppression of shedding of cell surface protein ectodomains in conditions characterized by an overactivity of such a shedding enzyme or enzymes would be of
10 benefit, and compounds which inhibit this cell surface protein ectodomain shedding would be useful and of benefit.

Accordingly it is another object of the present invention to provide a potent, orally active inhibitor of shedding of cell surface protein ectodomains acting via inhibition of one or more specific enzymes which mediate this proteolytic event.

15

SUMMARY OF THE INVENTION

In summary, the invention includes a family of compounds having the general structural formula:



20

(I)

or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof, wherein

W is a reverse hydroxamic acid group;

25 R₁ is a substituent other than hydrogen;

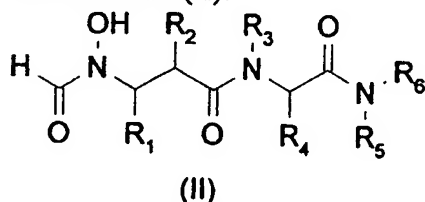
R₄ is a lipophilic substituent preferably with steric bulk proximal to the peptide backbone, and;

R₆ is a heteroaryl substituent.

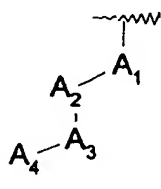
Such compounds are novel and are unknown in the art and, given the
30 appropriate choice of R₁, R₂, R₃, R₄, R₅, and R₆, show potent inhibition of MMP's, cell-free TNF convertase enzyme and TNF release from cells, and in some cases inhibit TNF convertase and TNF release from cells in preference to matrix metalloproteases. The heteroaryl nature of R₆ in combination with an appropriate choice of R₁, R₂, R₃, R₄, and R₅ is beneficial in achieving increased potency against

TNF release from cells relative to inhibition of MMP's. Such molecules are potentially selective for TNF inhibition over MMP's and may possess an improved therapeutic profile where inhibition of one or more of the matrix metalloproteases is associated with an adverse biological response or abnormal pathology. The heteroaryl nature of R_6 in combination with an appropriate choice of R_1 , R_2 , R_3 , R_4 , and R_5 is also beneficial in achieving selective inhibition of one or more of the matrix metalloproteases (for example, collagenase-3) in preference to TNF convertase inhibition and inhibition of TNF release from whole cells.

A more preferred group of compounds of the present invention include those of the formula (II):

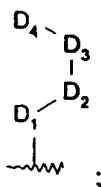


where R_1 is



- where A_1 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, or a direct bond;
 A_2 is $\text{C}(\text{O})\text{NR}_7$, $\text{NR}_7\text{C}(\text{O})$, SO_2NR_7 , NR_7SO_2 , NR_7 , S, SO, SO_2 , O, $\text{C}(\text{O})$, $\text{C}(\text{O})\text{O}$, $\text{OC}(\text{O})$, or a direct bond, where R_7 is as defined below;
 A_3 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, or a direct bond;
 A_4 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heteroaryl, aryl, NR_8R_9 , OR_8 , or hydrogen, where R_8 and R_9 are as defined below;

R_2 is



where D_1 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, $NR_{10}(O)C$, NR_{10} , S, SO, SO_2 , O, $O(O)C$, or a direct bond, where R_{10} is as defined below;

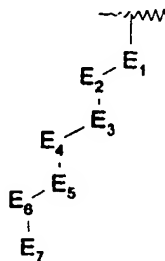
D_2 is S, SO, SO_2 , O, $C(O)$, $C(O)O$, $OC(O)$, $C(O)NR_{11}$, $NR_{11}C(O)$, NR_{11} , or a direct bond, where R_{11} is as defined below;

D_3 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, S, SO, SO_2 , O, $C(O)$, $C(O)O$, $OC(O)$, $C(O)NR_{12}$, $NR_{12}C(O)$, SO_2NR_{12} , $NR_{12}SO_2$, NR_{12} , or a direct bond, where R_{12} is as defined below;

D_4 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, OR_{13} , or hydrogen, where R_{13} is as defined below;

R_3 is hydrogen or lower alkyl;

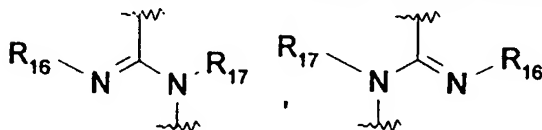
R_4 is



where E_1 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, $C(O)NR_{14}$, $NR_{14}C(O)$, $C(O)$, $C(O)O$, $OC(O)$, or a direct bond, where R_{14} is as defined below;

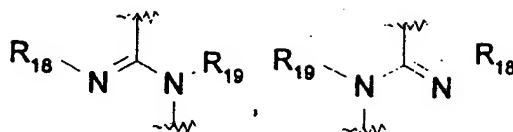
E_2 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{15} , S, SO, SO_2 , O, $C(O)$, $C(O)O$, $OC(O)$, or a direct bond, where R_{15} is as defined below;

E_3 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{16} , S, SO, SO_2 , O, $C(O)$, $C(O)O$, $OC(O)$,



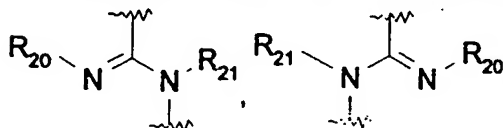
or a direct bond, where R_{16} and R_{17} are as defined below;

E_4 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{18} , S, SO, SO_2 , O, $C(O)$, $C(O)O$, $OC(O)$,



or a direct bond, where R_{18} and R_{19} are as defined below;

E_5 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{20} , S, SO, SO_2 , O, C(O), C(O)O, OC(O),



or a direct bond, where R_{20} and R_{21} are as defined below;

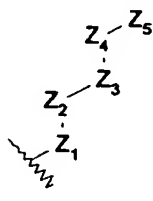
E_6 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{22} , S, SO, SO_2 , O, C(O), C(O)O, OC(O), or a direct bond, where R_{22} is as defined below;

- 10 E_7 is hydrogen, $NR_{23}R_{24}$, OR_{23} , SR_{23} , SOR_{23} , SO_2R_{23} , alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl, where R_{23} and R_{24} are as defined below;

R_5 is

- 15 hydrogen or lower alkyl;

R_6 is



where Z_1 is heteroarylene;

- 20 Z_2 is lower alkylene, lower alkenylene, lower alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, C(O) NR_{25} , NR_{25} C(O), SO_2NR_{25} , $NR_{25}SO_2$, NR_{25} , S, SO, SO_2 , O, C(O), C(O)O, OC(O), or a direct bond, where R_{25} is as defined below;

- 25 Z_3 is lower alkylene, lower alkenylene, lower alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, C(O) NR_{26} , NR_{26} C(O), SO_2NR_{26} , $NR_{26}SO_2$, NR_{26} , S, SO, SO_2 , O, C(O), C(O)O, OC(O), or a direct bond, where R_{26} is as defined below;

Z_4 is lower alkylene, lower alkenylene, lower alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, C(O) NR_{27} , NR_{27} C(O),

$\text{SO}_2\text{NR}_{27}$, $\text{NR}_{27}\text{SO}_2$, NR_{27} , S, SO, SO_2 , O, C(O), C(O)O, OC(O), or a direct bond, where R_{27} is as defined below;

Z_5 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heteroaryl, aryl, $\text{NR}_{28}\text{R}_{29}$, OR_{28} , or hydrogen, where R_{28} and R_{29} are as defined below;

5

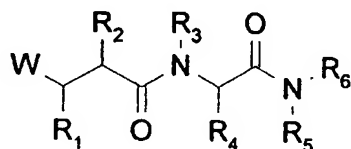
R_7 , R_8 , R_9 , R_{14} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , R_{28} , and R_{29} are, independently, hydrogen, alkyl, alkynyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, or heteroaryl;

10 R_{10} , R_{11} , R_{12} , and R_{13} are, independently, hydrogen, alkyl, alkynyl, alkenyl, cycloalkyl, cycloalkenyl, or heterocyclyl;

or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof.

15

Compounds of the present invention which are currently preferred for their high biological activity are listed below in Tables 1A, 1B and 1C; variables below are with reference to the generic structure (I):



20

(I)

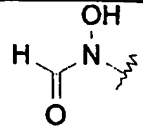
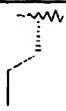
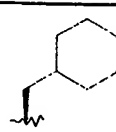
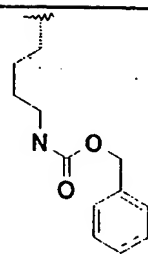
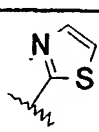
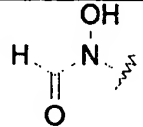

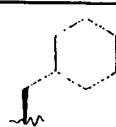
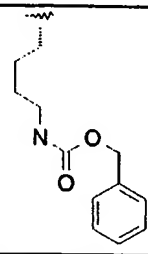
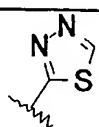
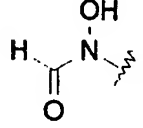
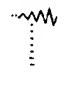
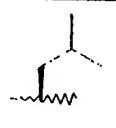
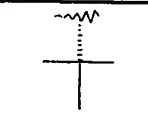

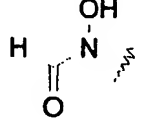
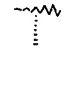
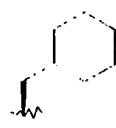
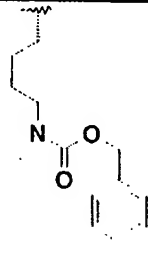
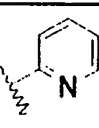
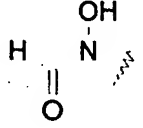


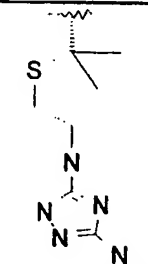

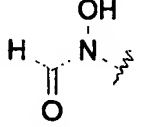
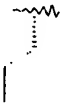



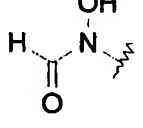

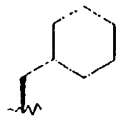
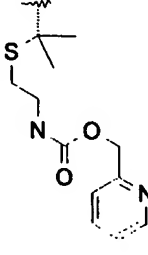

For the sake of clarity there is no Example 50 in Table 1A below.

Table 1A

10

Example	W	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
1				H		H	
2				H		H	
3				H		H	
4				H		H	
5				H		H	
6				H		H	

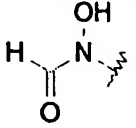

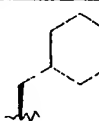
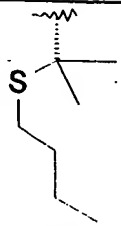

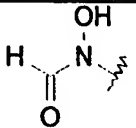
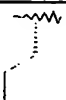

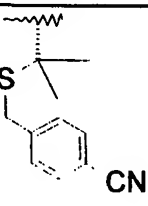
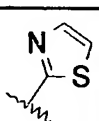
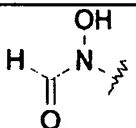

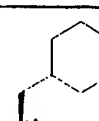
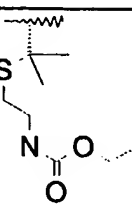
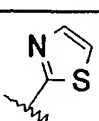
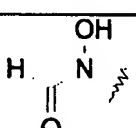
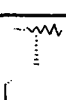
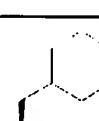
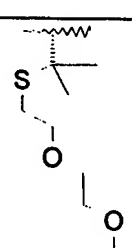
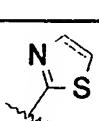
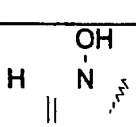


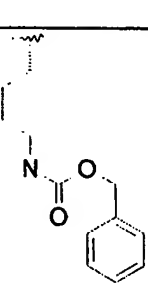
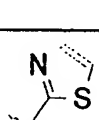
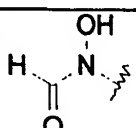

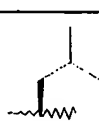
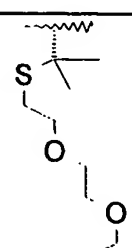
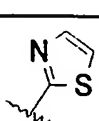
11

7				H		H	
8				H		H	
9				H		H	
10				H		H	
11				H		H	
12				H		H	
13				H		H	

12

14				H		H	
15				H		H	
16				H		H	
17				H		H	
18				H		H	
19				H		H	
20				H		H	

13

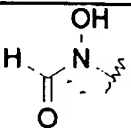
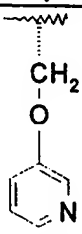
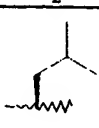
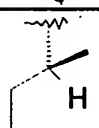
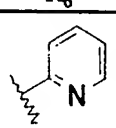
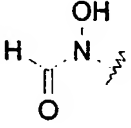


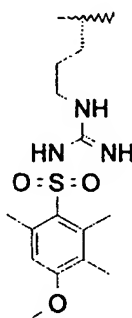
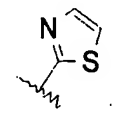
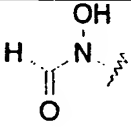
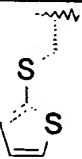
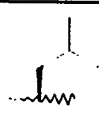
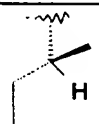
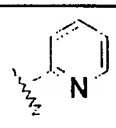
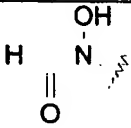
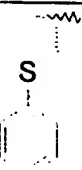

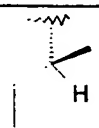

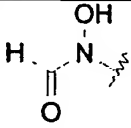

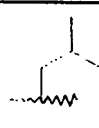

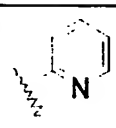
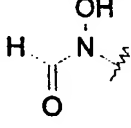

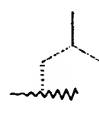
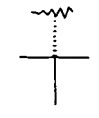
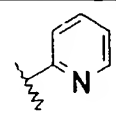
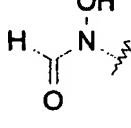

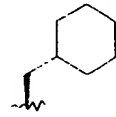
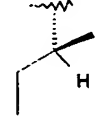
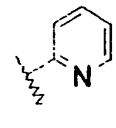
21				H		H	
22				H		H	
23				H		H	
24				H		H	
25				H		H	
26				H		H	

27				H		H	
28				H		H	
29				H		H	
30				H		H	
31				H		H	
32				H		H	
33				H		H	

34				H		H	
35				H		H	
36				H		H	
37				H		H	
38				H		H	
39				H		H	
40				H		H	
41				H		H	

Table 1A continued

16

Example	W	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
42				H		H	
43				H		H	
44				H		H	
45				H		H	
46				H		H	
47				H		H	
48				H		H	

49				H		H	
51				H		H	
52				H		H	
53				H		H	
54				H		H	
55				H		H	
56				H		H	

57				H		H	
58				H		H	
59				H		H	
60				H		H	
61				H		H	
62				H		H	
63				H		H	

Table 1A continued

19

Example	W	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
64				H		H	
65				H		H	
66				H		H	
67				H		H	
68				H		H	
69				H		H	

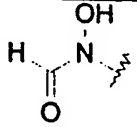


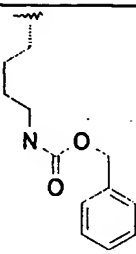
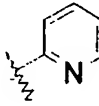
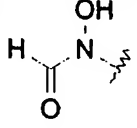

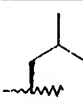
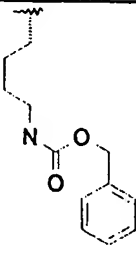
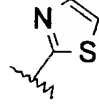
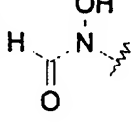

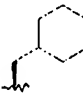
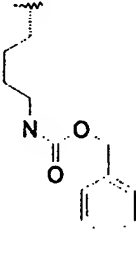
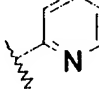
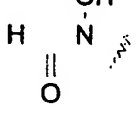

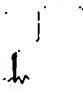
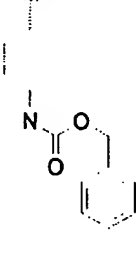
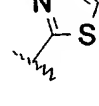
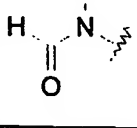


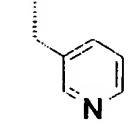
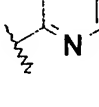
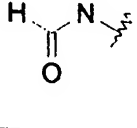



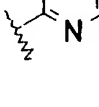
70				H		H	
71				H		H	
72				H		H	
73				H		H	
74				H		H	
75				H		H	

Table 1B

21

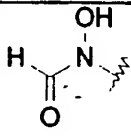

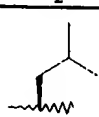
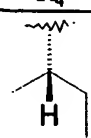
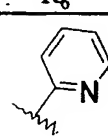
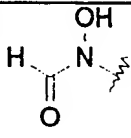

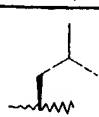
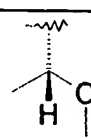
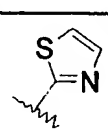
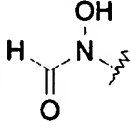

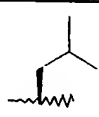
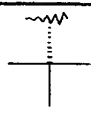
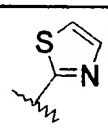
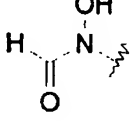

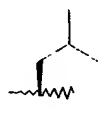
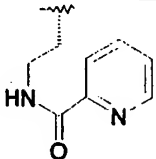
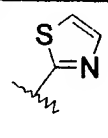
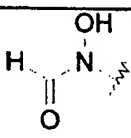



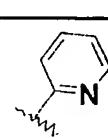
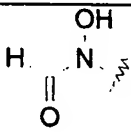



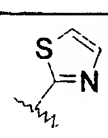
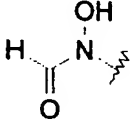

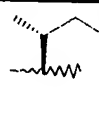

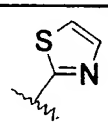
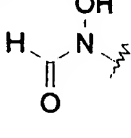

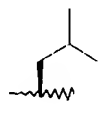

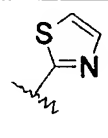
Example	W	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
76				H		H	
77				H		H	
78				H		H	
79				H		H	
80				H		H	
81				H		H	
82				H		H	
83				H		H	

Table 1C

22

Example	W	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
84				H		H	
85				H		H	
86				H		H	
87				H		H	
88				H		H	
89				H		H	
90				H		H	
91				H		H	
92				H		H	

93				H		H	
94				H		H	
95				H		H	
96				H		H	
97				H		H	
98				H		H	
99				H		H	
100				H		H	
101				H		H	

24

102				H		H	
103				H		H	
104				H		H	
105				H		H	

Example	W	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
106				H		H	
107				H		H	
108				H		H	
109				H		H	

25

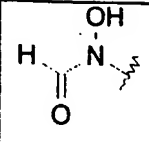

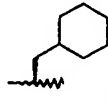
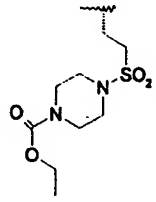
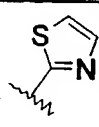
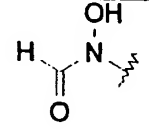

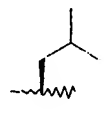
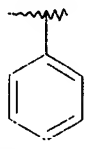
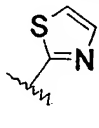
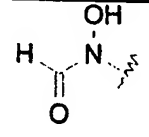

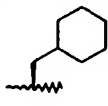
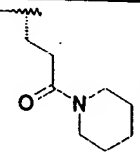
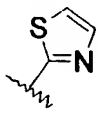
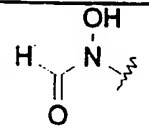

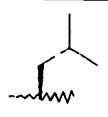

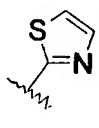
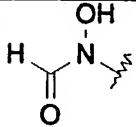

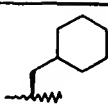

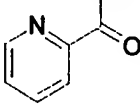
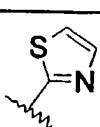
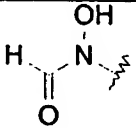

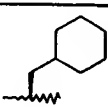

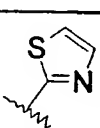
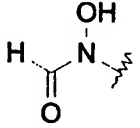

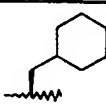

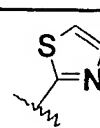
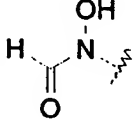
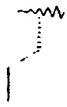
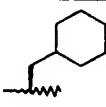

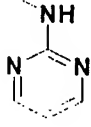
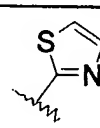
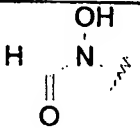
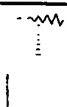
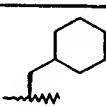

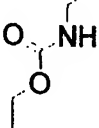
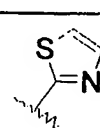
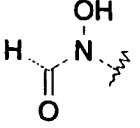

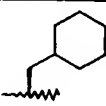

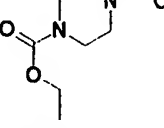
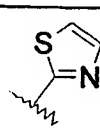
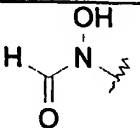

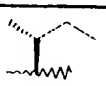

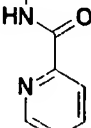
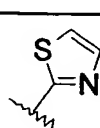
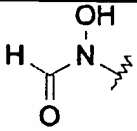

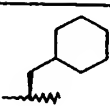
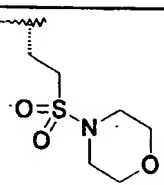
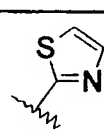
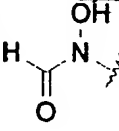

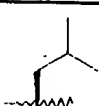
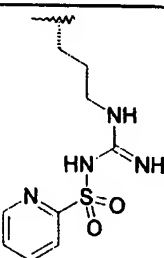
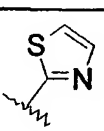
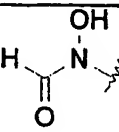
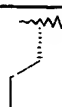
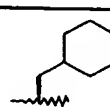
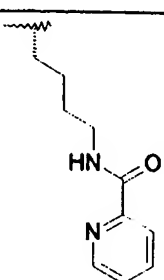
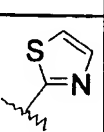
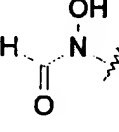
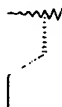
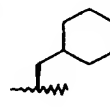
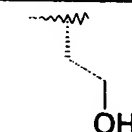
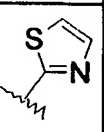
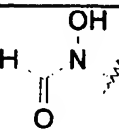
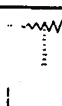
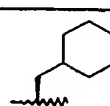
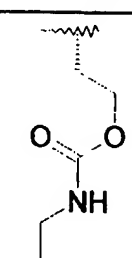
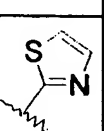
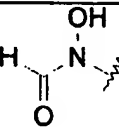

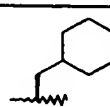
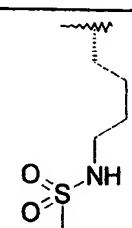
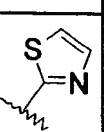
110				H		H	
111				H		H	
112				H		H	
113				H		H	

Table 1C continued

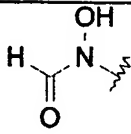

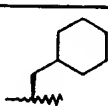
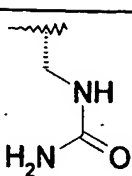
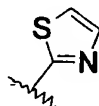
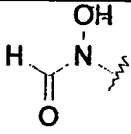

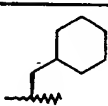
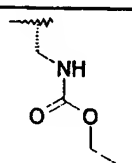
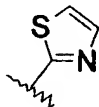
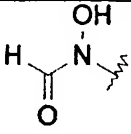

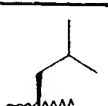
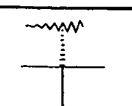
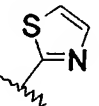
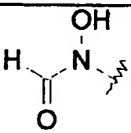

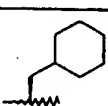
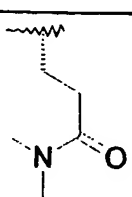
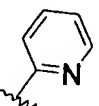
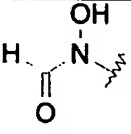

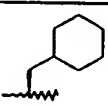
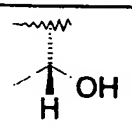
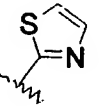
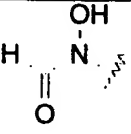
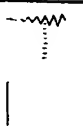
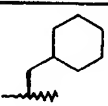
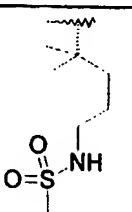
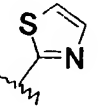
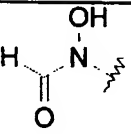

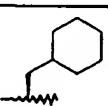
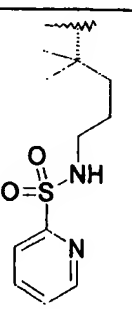
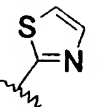
26

Example	W	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
114				H		H	
115				H		H	
116				H		H	
117				H		H	
118				H		H	
119				H		H	

120				H	 	H	
121				H	 OH	H	
122				H	 O	H	
123				H	 	H	
124				H	 	H	
125				H	 	H	
126				H	 	H	

127				H		H	
128				H		H	
129				H		H	
130				H		H	
131				H		H	
132				H		H	

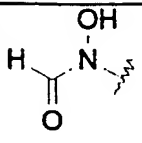

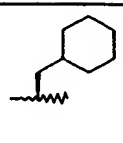
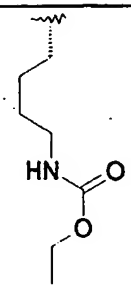
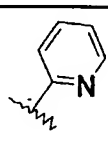
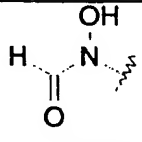

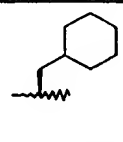
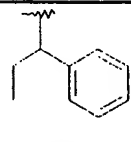
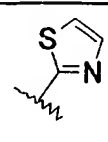
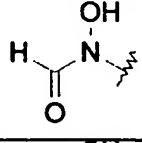

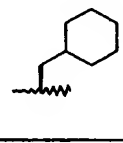
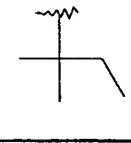
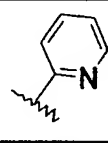
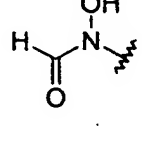

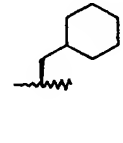
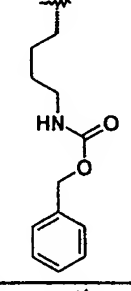
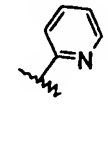
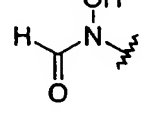
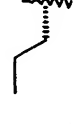
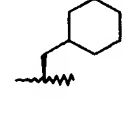

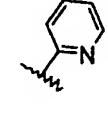
133				H		H	
134				H		H	
135				H		H	
136				H		H	
137				H		H	
138				H		H	
139				H		H	
140				H		H	

141				H		H	
142				H		H	
143				H		H	
144				H		H	
145				H		H	
146				H		H	
147				H		H	

148				H		H	
149				H		H	
150				H		H	
151				H		H	
152				H		H	
153				H		H	
154				H		H	
155				H		H	
156				H		H	

157				H		H	
158				H		H	
159				H		H	
160				H		H	
161				H		H	
162				H		H	
163				H		H	
164				H		H	
165				H		H	
166				H		H	

167				H		H	
168				H		H	
169				H		H	
170				H		H	
171				H		H	
172				H		H	
173				H		H	

174				H		H	
175				H		H	
176				H		H	
177				H		H	
178				H		H	

Compounds of the present invention which are currently preferred for their biological activity are listed by name below in Tables 2A, 2B and 2C.

For the sake of clarity there is no Example 50 in Table 2A below.

5

Table 2A

Example	Chemical Name
1	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide
2	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(1,3-pyrimidin-2-ylcarbamoyl)-1-pentyl]amide
3	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-(2-benzoyloxycarbonylamino-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
4	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-4-(1,3-Pyrimidin-2-yl)amino-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
5	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-butyl)hexanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
6	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-[(2 <i>R</i>)-2-butyl]butanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
7	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
8	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide
9	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
10	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)pentanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
11	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid

	[(1 <i>R</i>)-2-Methyl-2-((3-amino-1,2,4-triazol-5-ylamino)-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
12	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclopropylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3, thiazol-2-ylcarbamoyl)-1-propyl]amide
13	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-((2-pyridylmethoxycarbonylamino)-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
14	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-((2-pyridylmethoxycarbonylamino)-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
15	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-(3-cyclopentenyl)-1-ethyl)-hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3,thiazol-2-ylcarbamoyl)propyl]amide
16	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclopentylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3, thiazol-2-ylcarbamoyl)-1-propyl]amide
17	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(4-isopropyl-1-cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-propyl]amide
18	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-cyclopentyl-1-ethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3, thiazol-2-ylcarbamoyl)propyl]amide
19	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
20	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-(2-(cyanoimino-propylamino)methylamino-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
21	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-(1-butylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
22	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-(4-cyanobenzylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
23	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-(2-ethoxycarbonylamino-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
24	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-(2-(2-ethoxy)ethoxy)-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

25	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(3-pentyl)hexanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
26	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-(2-((2-ethoxy)ethoxy)-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)propyl]amide
27	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-(2-ethoxycarbonylamino-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]-amide
28	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-propyl]amide
29	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-methylsulfanyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
30	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-5-(2-Pyridylcarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
31	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-5-Ethoxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
32	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-4-(4-Trifluoromethyl-1,3-pyrimidin-2-yl)amino-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
33	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-5-(4-Trifluoromethyl-1,3-pyrimidin-2-yl)amino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
34	3-(Formyl-hydroxyamino)-2-cyclohexylhexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(2-pyridylcarbamoyl)-1-propyl]amide
35	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
36	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-5-Acetylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
37	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-5-cyclopentylacetylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
38	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-5-(3-methoxybenzoyl)amino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide

39	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2-(3-Pyridyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide
40	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
41	(2 <i>R</i> ,3 <i>S</i>)-4-Phenyl-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-4-(Imino-(2,3,6-trimethyl-4-methoxybenzenesulfonylamino))-methylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
42	(2 <i>R</i> ,3 <i>R</i>)-4-(3-Pyridyloxy)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
43	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-4-(Imino-(2,3,6-trimethyl-4-methoxybenzenesulfonylamino))-methylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
44	(2 <i>R</i> ,3 <i>R</i>)-4-(Thiophen-2-ylsulfanyl)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
45	(2 <i>R</i> ,3 <i>R</i>)-4-Phenylsulfanyl-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
46	3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i>)-2,2-dimethyl-1-(2-pyridylcarbamoyl)-1-propyl]amide
47	(2 <i>S</i> ,3 <i>R</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(2-pyridylcarbamoyl)-1-propyl]amide
48	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)pentanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
49	(2 <i>R</i> ,3 <i>S</i>)-5-Benzyloxy-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
51	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-2-(Thiophen-2-yl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide
52	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i>)-5-Benzyloxycarbonylamino-1-(5-methyl-1,2-isoxazol-3-ylcarbamoyl)-1-pentyl]amide
53	(2 <i>R</i> ,3 <i>R</i>)-4-Benzyloxy-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-5-Benzyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide

54	(2 <i>R</i> ,3 <i>R</i>)-4-Benzoyloxy-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
55	(2 <i>R</i> ,3 <i>S</i>)-7-Methyl-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)octanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
56	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(2-pyridylcarbamoyl)-1-propyl]amide
57	(2 <i>R</i> ,3 <i>S</i>)-4-Phenyl-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
58	(2 <i>R</i> ,3 <i>S</i>)-4-Phenyl-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
59	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-4-(Imino-(2,3,6-trimethyl-4-methoxybenzenesulfonylamino))methylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
60	(3 <i>S</i>)-4-Methyl-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
61	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
62	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-butyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(2-pyridylcarbamoyl)-1-propyl]amide
63	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-butyl)hexanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
64	(2 <i>R</i> ,3 <i>S</i>)-7-Methyl-3-(formyl-hydroxyamino)-2-(cyclohexylmethyl)octanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
65	(2 <i>R</i> ,3 <i>S</i>)-7-Methyl-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)octanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
66	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(2-pyridylcarbamoyl)-1-propyl]amide

67	(2 <i>R</i> ,3 <i>S</i>)-5-(2-Tetrahydrofuryl)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
68	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-5-Benzylloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
69	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(3-cyclohexyl-1-propyl)butanoic Acid [(1 <i>S</i>)-5-Benzylloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
70	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i>)-5-Benzylloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
71	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i>)-5-Benzylloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
72	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)butanoic Acid [(1 <i>S</i>)-5-Benzylloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
73	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)butanoic Acid [(1 <i>S</i>)-5-Benzylloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
74	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-2-(3-Pyridyl)-1-(2-pyridylcarbamoyl)-1-ethyl]amide
75	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(3-methyl-1-butyl)butanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(2-pyridylcarbamoyl)-1-propyl]amide

Table 2B

Example	Chemical Name
76	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
77	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
78	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
79	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1 <i>S</i>)-3-(2-Pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
80	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
81	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
82	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-[(2 <i>R</i>)-2-butyl]butanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
83	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide

Table 2C

Example	Chemical Name
84	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
85	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-butyl)butanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
86	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Hydroxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
87	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-butyl)butanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Hydroxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
88	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-(2-Pyridylmethoxy)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
89	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
90	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1 <i>S</i>)-3,3-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
91	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>R</i>)-2-Methyl-2-methylsulfenyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
92	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1 <i>R</i>)-2-Methyl-2-methylsulfenyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
93	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1 <i>S</i>)-3-(4-Morpholinesulfonyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
94	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1 <i>S</i>)-2-Methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
95	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-3-(4-Morpholinesulfonyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
96	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1 <i>S</i>)-3-(4-Morpholinesulfonyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
97	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid

	[(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
98	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1 <i>R</i>)-2-Methyl-2-methylsulfanyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
99	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Hydroxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
100	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2-(4-Ethoxycarbonylpiperazine-1-ylcarbonyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide
101	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid[(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
102	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-[(2 <i>R</i>)-2-butyl]butanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-5-ethoxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
103	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
104	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-[(2 <i>R</i>)-2-butyl]butanoic Acid [(1 <i>S</i> ,2 <i>S</i>)-2-Methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
105	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>S</i>)-4-(Amino-(methanesulfonylimino))methylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
106	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1 <i>S</i>)-4-(Amino-(methanesulfonylimino))methylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
107	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-3-(4-(2-Furyl)carbonylpiperazine-1-ylcarbonyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
108	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1 <i>S</i>)-3-Ethoxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
109	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-4-Ethoxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
110	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid

	[(1S)-3-(4-Ethoxycarbonylpiperazine-1-ylsulfonyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	
111	(2R,3S)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [1-Phenyl-1-(1,3-thiazol-2-ylcarbamoyl)methyl]amide	
112	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-3-(1-Piperidinylcarbonyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	
113	(2R,3S)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1S,2S)-2-methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide	
114	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-6,6,6-trifluorohexanoic Acid [(1S,2R)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	
115	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-6,6,6-trifluorohexanoic Acid [(1S,2R)-2-Hydroxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	
116	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1S)-3-(2-Pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	
117	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-3-(2-Pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	
118	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-3-(Imino(amino))methylaminoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	
119	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-5-(1,3-Pyrimidin-2-yl)amino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide	
120	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-4-(2-Pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide	
121	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1S)-2-Hydroxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide	
122	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1S)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide	

123	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-4-(1,3-Pyrimidin-2-yl)amino-1-(1,3-thiazol-2-ylcarbamoyl)-1- butyl]amide	Acid
124	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-5-Ethoxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1- pentyl]amide	Acid
125	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-3-(4-Ethoxycarbonylpiperazine-1-ylcarbonyl)-1-(1,3-thiazol-2- ylcarbamoyl)-1-propyl]amide	Acid
126	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-[(2 <i>R</i>)-2-butyl]butanoic (2-Pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide	Acid
127	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-3-(4-Morpholinesulfonyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1- propyl]amide	Acid
128	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic [(1 <i>S</i>)-4-(Imino-(2-pyridinesulfonylamino))methylamino-1-(1,3-thiazol-2- ylcarbamoyl)-1-butyl]amide	Acid
129	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-5-(2-Pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1- pentyl]amide	Acid
130	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-3-Hydroxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	Acid
131	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-3-Ethylcarbamoxyloxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	Acid
132	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-5-Methanesulfonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1- pentyl]amide	Acid
133	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-5-(2-Dimethylamino-1-ethoxycarbonylamino)-1-(1,3-thiazol-2- ylcarbamoyl)-1-pentyl]amide	Acid
134	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i> ,2 <i>S</i>)-2-Hydroxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide	Acid
135	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i> ,2 <i>R</i>)-2-(2-Pyridylmethoxy)-1-(1,3-thiazol-2-ylcarbamoyl)-1- propyl]amide	Acid
136	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic [(1 <i>S</i>)-2-Hydroxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide	Acid

137	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-3-Methylaminosulfonyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
138	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1 <i>S</i>)-2-(2-Pyridinesulfonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide
139	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-3-Dimethylaminosulfonyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
140	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1 <i>S</i>)-2-Acetylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide
141	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1 <i>S</i>)-2-Carbamoylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide
142	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1 <i>S</i>)-2-Ethoxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-ethyl]amide
143	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
144	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1 <i>S</i>)-3-Dimethylaminocarbonyl-1-(2-pyridinecarbonyl)-1-propyl]amide
145	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-3-cyclopropyl-2-(cyclohexylmethyl)propanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Hydroxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
146	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-5-methanesulfonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
147	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-5-(2-pyridylsulfonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
148	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-5-(2-pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
149	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-6,6,6-

	trifluorohexanoic Acid [(1S)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
150	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-2-Hydroxy-2-methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
151	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-2,2-Dimethyl-1-(2-pyrazinecarbamoyl)-1-propyl]amide
152	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-2,2-Dimethyl-1-(4-aminopyrimidin-2-ylcarbamoyl)-1-propyl]amide
153	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-3-Dimethylaminocarbonyl-1-(2-pyridylcarbamoyl)-1-propyl]amide
154	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-2,2-Dimethyl-1-(5-methyl-1,3,4-thiadiazol-2-ylcarbamoyl)-1-propyl]amide
155	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S,2S)-2-Methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
156	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-2,2-Dimethyl-1-(3-aminopyridin-2-ylcarbamoyl)-1-propyl]amide
157	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S,2R)-2-Hydroxy-1-(2-pyridylcarbamoyl)-1-propyl]amide
158	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1R)-2-Methyl-2-methylsulfenyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
159	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)-4-methylpentanoic Acid [(1S)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
160	(2R,3S)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1S,2S)-2-Methyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
161	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-3-Methylsulfonyl-1-(2-pyridylcarbamoyl)-1-propyl]amide
162	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-2,2-Dimethyl-1-(3-pyridylcarbamoyl)-1-propyl]amide
163	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1S)-2,2-Dimethyl-1-(4-pyridylcarbamoyl)-1-propyl]amide
164	(2R,3S)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid

	[(1 <i>S</i> ,2 <i>R</i>)-2-(2-Methyl-1-propyloxy)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
165	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-(2-Methyl-1-propyloxy)-1-(2-pyridylcarbamoyl)-1-propyl]amide
166	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2-(4-Fluorophenyl)-1-(2-pyridinecarbamoyl)-1-ethyl]amide
167	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Methoxy-1-(2-pyridylcarbamoyl)-1-propyl]amide
168	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-5-(2-Pyridylsulfonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
169	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-5-(Ethoxycarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide
170	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclobutylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
171	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i> ,2 <i>R</i>)-2-Benzoyloxy-1-(2-pyridylcarbamoyl)-1-propyl]amide
172	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1 <i>R</i>)-2-Methyl-2-methylsulfenyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide
173	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-5-(2-Pyridylcarbonylamino)-1-(2-pyridylcarbamoyl)-1-pentyl]amide
174	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-5-Ethoxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
175	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [2-Phenyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
176	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [2,2-Dimethyl-1-(2-pyridylcarbamoyl)-1-butyl]amide
177	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-5-Benzoyloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide
178	(2 <i>R</i> ,3 <i>S</i>)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1 <i>S</i>)-2,2-Dimethyl-1-(2-pyridylcarbamoyl)-1-propyl]amide

Preferred embodiments of the invention include compounds of general formula (II) as defined above or pharmaceutically acceptable salts, solvates, biohydrolyzable esters, biohydrolyzable amides, affinity reagents, or prodrugs thereof

5 where

R₁ is methyl, ethyl, isopropyl, benzyl, 2-benzyloxy-1-ethyl, benzyloxymethyl, 2-tetrahydrofuryl-1-ethyl, 2-thiophenesulfanylmethyl, benzenesulfanylmethyl, 3-pyridyloxymethyl or n-propyl;

10 R₂ is isobutyl, 3-methyl-1-butyl, sec-butyl, cyclohexylmethyl, cyclopentylmethyl, 2-methyl-1-butyl, cyclohexyl, cyclopentylmethyl, or 2-(3-cyclopentenyl)-1-ethyl;

R₃ is hydrogen;

15 R₄ is tert-butyl, 2-thiophenemethyl, sec-butyl, 1-methoxy-1-ethyl, 4-(benzyloxycarbonylamino)-1-butyl, 4-(ethoxycarbonylamino)-1-butyl, 4-acetylamino-1-butyl, 4-cyclopentylacetylamino-1-butyl, 4-(3-methoxybenzoylamino)-1-butyl, 3-pyridylmethyl, 4-(2-pyridylmethoxycarbonylamino)-1-butyl, 2-(2-(benzyloxycarbonylamino)ethylsulfanyl)-2-propyl, 2-(2-(ethoxycarbonylamino)-1-ethylsulfanyl)-2-propyl, 2-(2-(cyanoimino-propylamino)methylamino)-1-ethylsulfanyl)-2-propyl, 3-(pyrimidin-2-ylamino)-1-propyl, 3-(4-trifluoromethylpyrimidin-2-ylamino)-1-propyl, 4-(4-trifluoromethylpyrimidin-2-ylamino)-1-butyl or 3-(imino-(1,2,6-trimethyl-4-methoxybenzenesulfonylamino))-methylamino-1-propyl;

20

25

R₅ is hydrogen; and

R₆ is 2-thiazolyl, 2-pyridyl or 2-(1,3,4-thiadiazolyl);

30 Further preferred embodiments of the invention include compounds of general formula (II) as defined above or pharmaceutically acceptable salts, solvates, biohydrolyzable esters, biohydrolyzable amides, affinity reagents, or prodrugs thereof where

R₁ is 3,3,3-trifluoro-n-propyl, or cyclopropyl;

35

R₂ is cyclobutylmethyl;

R₃ is hydrogen;

R₄ is isopropyl, 1-hydroxy-1-ethyl, 2-(2-pyridylcarbonylamino)-1-ethyl, 1-(2-pyridylmethoxy)-1-ethyl, 2,2-dimethyl-1-propyl, 2-methylsulfenyl-2-propyl, 2-methylsulfanyl-2-propyl, 2-(4-morpholinesulfonyl)-1-ethyl, (4-ethoxycarbonylpiperazine-1-ylcarbonyl)methyl, 4-ethoxycarbonylamino-1,1-dimethyl-1-butyl, 3-(imino-(methanesulfonylamino))methylamino-1-propyl, 2-(4-(2-furyl)carbonylpiperazine-1-ylcarbonyl)ethyl, 2-ethoxycarbonylamino-1-ethyl, 3-ethoxycarbonylamino-1-propyl, 2-(4-ethoxycarbonylpiperazine-1-ylsulfonyl)-1-ethyl, phenyl, 2(1-piperidinecarbonyl)-1-ethyl, 2-(imino-(amino))methylaminoxy-1-ethyl, 4-(1,3-pyrimidin-2-yl)amino-1-butyl, 3-(2-pyridinecarbonylamino)-1-propyl, hydroxymethyl, methoxymethyl, 4-ethoxycarbonylamino-1-butyl, 2-(4-ethoxycarbonylpiperazine-1-ylcarbonyl)-1-ethyl, 4-(2-pyridinecarbonylamino)-1-butyl, 3-(imino-(2-pyridinesulfonylamino))methylamino-1-propyl, 2-hydroxy-1-ethyl, 2-(ethylcarbamoyloxy)-1-ethyl, 4-methanesulfonylamino-1-butyl, 4-(2-dimethylamino-1-ethoxycarbonylamino)-1-butyl, 2-methylaminosulfonyl-1-ethyl, 2-pyridinesulfonylaminomethyl, 2-dimethylaminosulfonyl-1-ethyl, acetylaminomethyl, carbamoylaminomethyl, ethoxycarbonylaminomethyl, 2-(dimethylaminocarbonyl)-1-ethyl, 4-methanesulfonylamino-1,1-dimethyl-1-butyl, 4-(2-pyridinesulfonylamino)-1,1-dimethyl-1-butyl, 4-(2-pyridinecarbonylamino)-1,1-dimethyl-1-butyl, 2-hydroxy-2-propyl, 2-(methylsulfonyl)-1-ethyl, 1-(2-methyl-1-propyloxy)-1-ethyl, 4-fluorobenzyl, 4-(2-pyridinesulfonylamino)-1-butyl, 1-benzyloxy-1-ethyl, 1-phenyl-1-propyl, or 1,1-dimethyl-1-propyl;

R₅ is hydrogen; and

R₆ is 3-pyridyl, 4-pyridyl, 3-amino-2-pyridyl, 2-pyrimidinyl, 4-amino-2-pyrimidinyl, 2-pyrazinyl, 3-(5-methylisoxazolyl), or 2-(5-methyl-1,3,4-thiadiazolyl).

According to a more preferred embodiment of the invention R₁ is methyl, ethyl, isopropyl, n-propyl or 3,3,3-trifluoro-n-propyl.

According to a further more preferred embodiment of the invention R₂ is isobutyl or sec-butyl.

According to a further more preferred embodiment of the invention R₃ is hydrogen.

According to a further more preferred embodiment of the invention R₄ is tert-butyl, sec-butyl, 1-methoxy-1-ethyl or 2-(2-pyridylcarbonylamino)-1-ethyl.

According to a further more preferred embodiment of the invention R_5 is hydrogen.

According to a further more preferred embodiment of the invention R_6 is 2-thiazolyl or 2-pyridyl.

A group of particularly preferred embodiments of the invention are those comprising Examples 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

Another group of particularly preferred embodiments of the invention are those comprising Examples 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

Another group of particularly preferred embodiments of the invention are those comprising Examples 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30.

Another group of particularly preferred embodiments of the invention are those comprising Examples 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40.

Another group of particularly preferred embodiments of the invention are those comprising Examples 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50.

Another group of particularly preferred embodiments of the invention are those comprising Examples 51, 52, 53, 54, 55, 56, 57, 58, 59 or 60.

Another group of particularly preferred embodiments of the invention are those comprising Examples 61, 62, 63, 64, 65, 66, 67, 68, 69 or 70.

Another group of particularly preferred embodiments of the invention are those comprising Examples 71, 72, 73, 74 or 75.

Another group of particularly preferred embodiments of the invention are those comprising Examples 76, 77, 78, 79, 80, 81, 82 or 83.

Another especially preferred embodiment of the invention is that comprising Example 35.

Another especially preferred embodiment of the invention is that comprising Example 76.

The compounds of the present invention are inhibitors of matrix metalloproteases, TNF converting enzyme, and TNF activity from whole cells. The compounds of the present invention may also inhibit shedding of pathologically significant cell surface protein ectodomains. The invention described herein is additionally directed to pharmaceutical compositions and methods of inhibiting matrix metalloprotease and/or TNF activity in a mammal, which methods comprise administering to a mammal in need of a therapeutically defined amount of a compound of formula (I) or (II), defined above, as a single or polymorphic crystalline form or forms, an amorphous form, a solvate, a pharmaceutically acceptable salt, a solvate, a prodrug, a biohydrolyzable ester, or a biohydrolyzable amide thereof.

Certain compounds of formula (I) or (II), defined above, may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism). The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formulae (I) or (II) may exist in tautomeric forms other than that shown in the formulae and these are also included within the scope of the present invention.

Certain examples of the invention also are orally bioavailable in animals and possess oral activity in animal models of disease.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate.

Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of formula (I) or (II) and these form a further aspect of the invention.

Also included within the scope of the invention are the individual enantiomers of the compounds represented by formula (I) or (II) above as well as any wholly or partially racemic mixtures thereof. The present invention also covers the individual enantiomers of the compounds represented by formula above as mixtures with diastereoisomers thereof in which one or more of the three stereocenters are inverted.

According to a further aspect of the present invention there is provided a compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof for use in therapy.

According to a further aspect of the present invention there is provided the use

of a compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof in the preparation of a medicament for inhibiting the cellular release of tumour necrosis factor alpha.

- 5 According to a further aspect of the present invention there is provided the use of a compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof in the preparation of a medicament for inhibiting a matrix metalloprotease.

- 10 According to a further aspect of the present invention there is provided the use of a compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof in the preparation of a medicament for inhibiting the shedding of cell surface protein ectodomains.

- 15 According to a further aspect of the present invention there is provided the use of a compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof in the preparation of a medicament for inhibiting the growth of tumour metastases, or for the treatment of diabetes, or for the treatment of arthritis.

- 20 According to a further aspect of the present invention there is provided a method of inhibiting the cellular release of tumour necrosis factor alpha in a mammalian subject which comprises administering to said subject an effective amount of a compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof.

- 25 According to a further aspect of the present invention there is provided a method of inhibiting a matrix metalloprotease in a mammalian subject which comprises administering to said subject an effective amount of a compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof.

- 30 According to a further aspect of the present invention there is provided a method of inhibiting the shedding of cell surface protein ectodomains in a mammalian subject which comprises administering to said subject an effective amount of a compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof.

- 35 According to a further aspect of the present invention there is provided a method of inhibiting the growth of tumour metastases, or a method for the treatment

of diabetes, or a method for the treatment of arthritis, in a mammalian subject which comprises administering to said subject an effective amount of a compound of formula (II) as defined above or a pharmaceutically acceptable salt; solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof.

5

As used herein, the term "lower" refers to a group having between one and six carbons.

As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, n-butyl, n-pentyl, isobutyl, and isopropyl, and the like.

10

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, and the like.

20

25

As used herein, the term "alkenyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon double bond, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed.

30

As used herein, the term "alkenylene" refers to an straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon double bonds, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally

35

substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkenylene" as used herein include, but are not limited to, ethene-1,2-diyl, propene-1,3-diyl, methylene-1,1-diyl, and the like.

As used herein, the term "alkynyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon triple bond, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed.

As used herein, the term "alkynylene" refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon triple bonds, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkynylene" as used herein include, but are not limited to, ethyne-1,2-diyl, propyne-1,3-diyl, and the like.

As used herein, "cycloalkyl" refers to a alicyclic hydrocarbon group with one or more degrees of unsaturation, having from three to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and the like.

As used herein, the term "cycloalkylene" refers to a non-aromatic alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano,

halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

5 As used herein, the term "cycloalkenyl" refers to a substituted alicyclic hydrocarbon radical having from three to twelve carbon atoms and at least one carbon-carbon double bond in the ring system, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkenylene" as used herein include, but are not limited to, 1-cyclopentene-3-yl, 1-cyclohexene-3-yl, 1-cycloheptene-4-yl, and the like.

15 As used herein, the term "cycloalkenylene" refers to a substituted alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms and at least one carbon-carbon double bond in the ring system, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkenylene" as used herein include, but are not limited to, 4,5-cyclopentene-1,3-diyl, 3,4-cyclohexene-1,1-diyl, and the like.

25 As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO₂, O, or N, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "heterocyclylene" refers to a three to twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO₂, O, or N, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like.

As used herein, the term "aryl" refers to a benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. Examples of aryl include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, biphenyl, and the like.

As used herein, the term "arylene" refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "heteroaryl" refers to a five - to seven - membered aromatic ring, or to a polycyclic heterocyclic aromatic ring, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and

sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring systems, one or more of the rings may contain one or more heteroatoms. Examples of "heteroaryl" used herein are furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, and indazole, and the like.

As used herein, the term "heteroarylene" refers to a five - to seven - membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,4-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" refers to the group R_aO- , where R_a is alkyl.

As used herein, the term "alkenyloxy" refers to the group R_aO- , where R_a is alkenyl.

As used herein, the term "alkynyloxy" refers to the group R_aO- , where R_a is alkynyl.

As used herein, the term "alkylsulfanyl" refers to the group R_aS- , where R_a is alkyl.

As used herein, the term "alkenylsulfanyl" refers to the group R_aS- , where R_a is alkenyl.

As used herein, the term "alkynylsulfanyl" refers to the group R_aS- , where R_a is alkynyl.

5 As used herein, the term "alkylsulfenyl" refers to the group $R_aS(O)-$, where R_a is alkyl.

As used herein, the term "alkenylsulfenyl" refers to the group $R_aS(O)-$, where R_a is alkenyl.

10 As used herein, the term "alkynylsulfenyl" refers to the group $R_aS(O)-$, where R_a is alkynyl.

As used herein, the term "alkylsulfonyl" refers to the group R_aSO_2- , where R_a is alkyl.

As used herein, the term "alkenylsulfonyl" refers to the group R_aSO_2- , where R_a is alkenyl.

15 As used herein, the term "alkynylsulfonyl" refers to the group R_aSO_2- , where R_a is alkynyl.

As used herein, the term "acyl" refers to the group $R_aC(O)-$, where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyl" refers to the group $R_aC(O)-$, where R_a is aryl.

20 As used herein, the term "heteroaroyl" refers to the group $R_aC(O)-$, where R_a is heteroaryl.

As used herein, the term "alkoxycarbonyl" refers to the group $R_aOC(O)-$, where R_a is alkyl.

25 As used herein, the term "acyloxy" refers to the group $R_aC(O)O-$, where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyloxy" refers to the group $R_aC(O)O-$, where R_a is aryl.

As used herein, the term "heteroaroyloxy" refers to the group $R_aC(O)O-$, where R_a is heteroaryl.

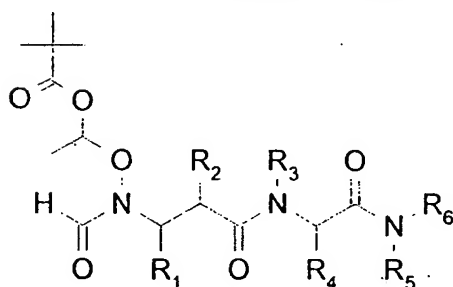
30 As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed.

35 As used herein, the terms "contain" or "containing" can refer to in-line substitutions at any position along the above-defined alkyl, alkenyl, alkynyl or

5 Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Solvents may be, by way of example, water, ethanol, or acetic acid.

10 a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable ester is orally absorbed from the gut and is transformed to (I) or (II)
15 in plasma. Many examples of such are known in the art and include by way of example lower alkyl esters, lower acyloxy-alkyl esters, lower alkoxyacyloxyalkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters. An example of such a biohydrolyzable ester applied to the general formula (II) is illustrated below in general formula (III).



(111)

a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable amide is orally absorbed from the gut and is transformed to (I) or (II) in plasma. Many examples of such are known in the art and include by way of example lower alkyl amides, α -amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides.

As used herein, the term "prodrug" includes biohydrolyzable amides and biohydrolyzable esters and also encompasses a) compounds in which the biohydrolyzable functionality in such a prodrug is encompassed in the compound of formula (I) or (II): for example, the lactam formed by a carboxylic group in R₂ and an amine in R₄, and b) compounds which may be oxidized or reduced biologically at a given functional group to yield drug substances of formula (I) or (II). Examples of these functional groups are, but are not limited to, 1,4-dihydropyridine, N-alkylcarbonyl-1,4-dihydropyridine, 1,4-cyclohexadiene, tert-butyl, and the like.

As used herein, the term "affinity reagent" is a group attached to the compound of formula (I) or (II) which does not affect its in vitro biological activity, allowing the compound to bind to a target, yet such a group binds strongly to a third component allowing a) characterization of the target as to localization within a cell or other organism component, perhaps by visualization by fluorescence or radiography, or b) facile separation of the target from an unknown mixture of targets, whether proteinaceous or not proteinaceous. An example of an affinity reagent according to b) would be biotin either directly attached to (I) or (II) or linked with a spacer of one to 50 atoms selected from the group consisting of C, H, O, N, S, or P in any combination. An example of an affinity reagent according to a) above would be fluorescein, either directly attached to (I) or (II) or linked with a spacer of one to 50 atoms selected from the group consisting of C, H, O, N, S, or P in any combination.

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

Whenever the terms "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. arylalkoxyaryloxy) they shall be interpreted as including those limitations given above for "alkyl" and "aryl". Alkyl or cycloalkyl substituents shall be recognized as being functionally equivalent to those having one or more degrees of unsaturation. Designated numbers of carbon atoms (e.g. C₁₋₁₀) shall refer independently to the number of carbon atoms in an alkyl, alkenyl or alkynyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which the term "alkyl" appears as its prefix root.

As used herein, the term "oxo" shall refer to the substituent =O.

As used herein, the term "halogen" or "halo" shall include iodine, bromine, chlorine and fluorine.

As used herein, the term "mercapto" shall refer to the substituent -SH.

As used herein, the term "carboxy" shall refer to the substituent -COOH.

As used herein, the term "cyano" shall refer to the substituent -CN.

As used herein, the term "aminosulfonyl" shall refer to the substituent -SO₂NH₂.

As used herein, the term "carbamoyl" shall refer to the substituent -C(O)NH₂.

As used herein, the term "sulfanyl" shall refer to the substituent -S-.

5 As used herein, the term "sulfenyl" shall refer to the substituent -S(O)-.

As used herein, the term "sulfonyl" shall refer to the substituent -S(O)₂-.

The compounds of formulae (I) and (II) can be prepared readily according to the following reaction Schemes (in which all variables are as defined before) and
10 Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

The most preferred compounds of the invention are any or all of those
15 specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known
20 variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

Abbreviations used in the Examples are as follows:

	g	= grams
25	mg	= milligrams
	L	= liters
	mL	= milliliters
	psi	= pounds per square inch
	M	= molar
30	N	= normal
	mM	= millimolar
	i.v.	= intravenous
	p.o.	= per oral
	s.c.	= subcutaneous
35	Hz	= hertz
	mol	= moles
	mmol	= millimoles

	mbar	= millibar
	rt	= room temperature
	min	= minutes
	h	= hours
5	d	= days
	mp	= melting point
	TLC	= thin layer chromatography
	R _f	= relative TLC mobility
	MS	= mass spectrometry
10	NMR	= nuclear magnetic resonance spectroscopy
	APCI	= atmospheric pressure chemical ionization
	ESI	= electrospray ionization
	m/z	= mass to charge ratio
	t _r	= retention time
15	ether	= diethyl ether
	MeOH	= methanol
	EtOAc	= ethyl acetate
	TEA	= triethylamine
	DIEA	= diisopropylethylamine
20	BOP	= (1-benzotriazolyl)tris(dimethylamino)phosphonium hexafluorophosphate
	THF	= tetrahydrofuran
	DMF	= N, N-dimethylformamide
	DMSO	= dimethylsulfoxide
25	LAH	= lithium aluminum hydride
	TFA	= trifluoroacetic acid
	EDC	= 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride
	HOBt	= 1-hydroxybenzotriazole
	LDA	= lithium diisopropylamide
30	THP	= tetrahydropyranyl
	NMM	= N-methylmorpholine, 4-methylmorpholine
	HMPA	= hexamethylphosphoric triamide
	DMPU	= 1,3-dimethylpropylene urea
	ppm	= parts per million
35	kD	= kiloDalton
	LPS	= lipopolysaccharide
	PMA	= phorbol myristate acetate

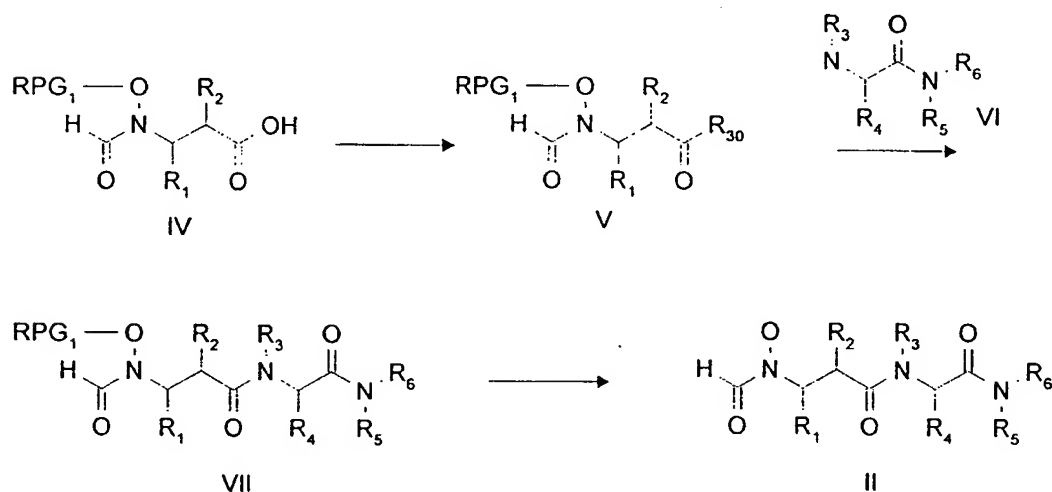
- SPA = scintillation proximity assay
 EDTA = ethylenediamine tetraacetic acid
 FBS = fetal bovine serum
 PBS = phosphate buffered saline solution
 5 ELISA = enzyme - linked immunosorbent assay

- Several of the following examples represent pairs of stereoisomers which were separated as diastereoisomers but were not identified therein. Determination and/or preparation of the R and S isomers could advantageously be approached by stereoselective chemical methods, see "Advanced Organic Chemistry", Carey and Sundberg, 3rd edition, Plenum Press, 1990, 596, by analytical methods such as X-ray crystallography, or by determination of biological activity and subsequent correlation to biologically active compounds of known stereochemistry.

15 GENERAL REACTION SCHEMES

Compounds of the invention may be prepared by methods known in the art, where such a method is shown in reaction Scheme 1.

Reaction Scheme 1



20

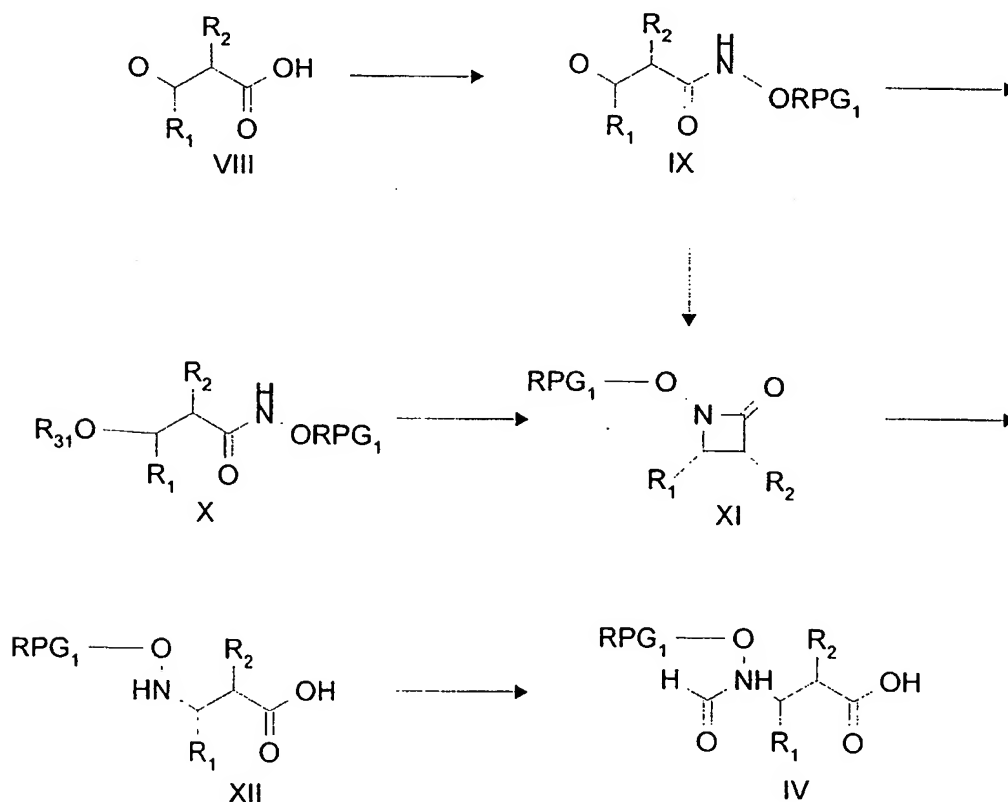
R₁, R₂, R₃, R₄, R₅, and R₆ are defined as for formula (II).

RPG₁ is a protecting group suitable for the hydroxylamine oxygen, such as benzyl or 2-tetrahydropyranyl.

R₃₀ is chosen from the group consisting of hydroxyl, O-C₆F₅, or halogen.

- When R_{30} is hydroxyl, the conversion of (V) to (VII) involves methods known in peptide chemistry; for example, the reaction may be conducted using HOBt in combination with a dehydrating agent such as dicyclohexylcarbodiimide in a suitable solvent, such as DMF. When R_{30} is $O-C_6F_5$, the conversion of (IV) to (V) is conducted by treating (IV) in a suitable solvent such as dichloromethane with pentafluorophenyl trifluoroacetate in the presence of pyridine, or with EDC and pentafluorophenol in a suitable solvent such as dichloromethane. The displacement reaction to produce (VII) is carried out in the presence of a suitable solvent such as dioxane, THF, dichloromethane, or DMF, at a temperature of 0 °C to 140 °C. The reaction is effected in the presence of an organic base such as NMM or triethylamine. The removal of the RPG_1 group where RPG_1 is benzyl may be achieved by hydrogenation of (VII) with palladium on barium sulfate in a suitable solvent such as ethanol or THF, or, where RPG_1 is 2-tetrahydropyranyl, by hydrolysis with aqueous acetic acid at a temperature of 20 °C to 100 °C.
- Reaction Scheme 2 depicts the synthesis of a compound of formula (IV).

Reaction Scheme 2



R_1 and R_2 are as defined for formula (II).

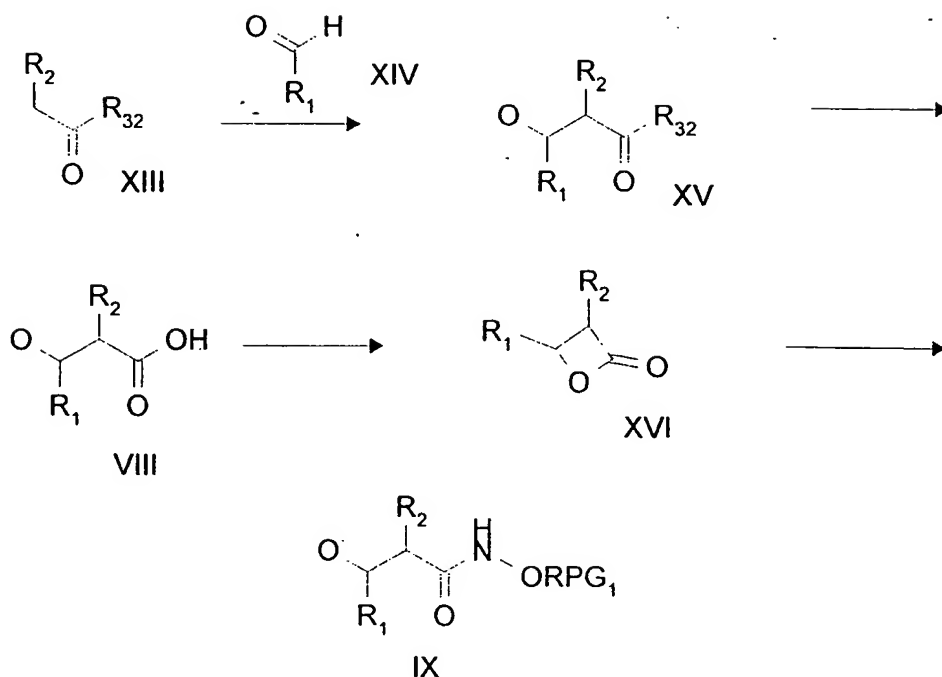
$R_{31}O$ is a nucleofugal group such as methanesulfonate or p-toluenesulfonate.

RPG_1 is as defined for reaction Scheme 1.

The acid of formula (VIII) may be converted to the alcohol of formula (IX) by treatment with HOBt, O-benzylhydroxylamine hydrochloride or O-(2-tetrahydropyranyl)hydroxylamine, NMM, and a carbodiimide reagent such as EDC in a suitable solvent such as DMF. The alcohol of formula (IX) may be converted to (X) by treatment with methanesulfonyl chloride or p-toluenesulfonyl chloride and pyridine in a suitable solvent such as dichloromethane. The conversion of (X) to (XI) may be conducted by treatment with potassium carbonate in a suitable solvent such as acetone or 2-butanone, at temperature of 20 °C to 90 °C. Alternatively, (IX) may be converted directly to (XI) by treatment with triphenylphosphine and diethyl azodicarboxylate or another azodicarbonyl diester or diamide in a suitable solvent such as THF at a temperature of -78 °C to 50 °C. The compound of formula (XI) may be converted to (XII) by treatment with an inorganic base such as sodium hydroxide in water or water in combination with a water - soluble organic cosolvent such as MeOH or THF, followed by acidification with an acidic solution such as aqueous citric acid or aqueous sodium bisulfate. The compound of formula (XII) may be converted to (IV) by treatment with acetic anhydride and formic acid or by treatment with formic acetic anhydride in pyridine in the presence or absence of a suitable cosolvent such as dichloromethane.

An alternative route of preparation of compounds of formula (IX) is depicted in reaction Scheme 3.

Reaction Scheme 3



RPG₁ is as defined for reaction Scheme 1.

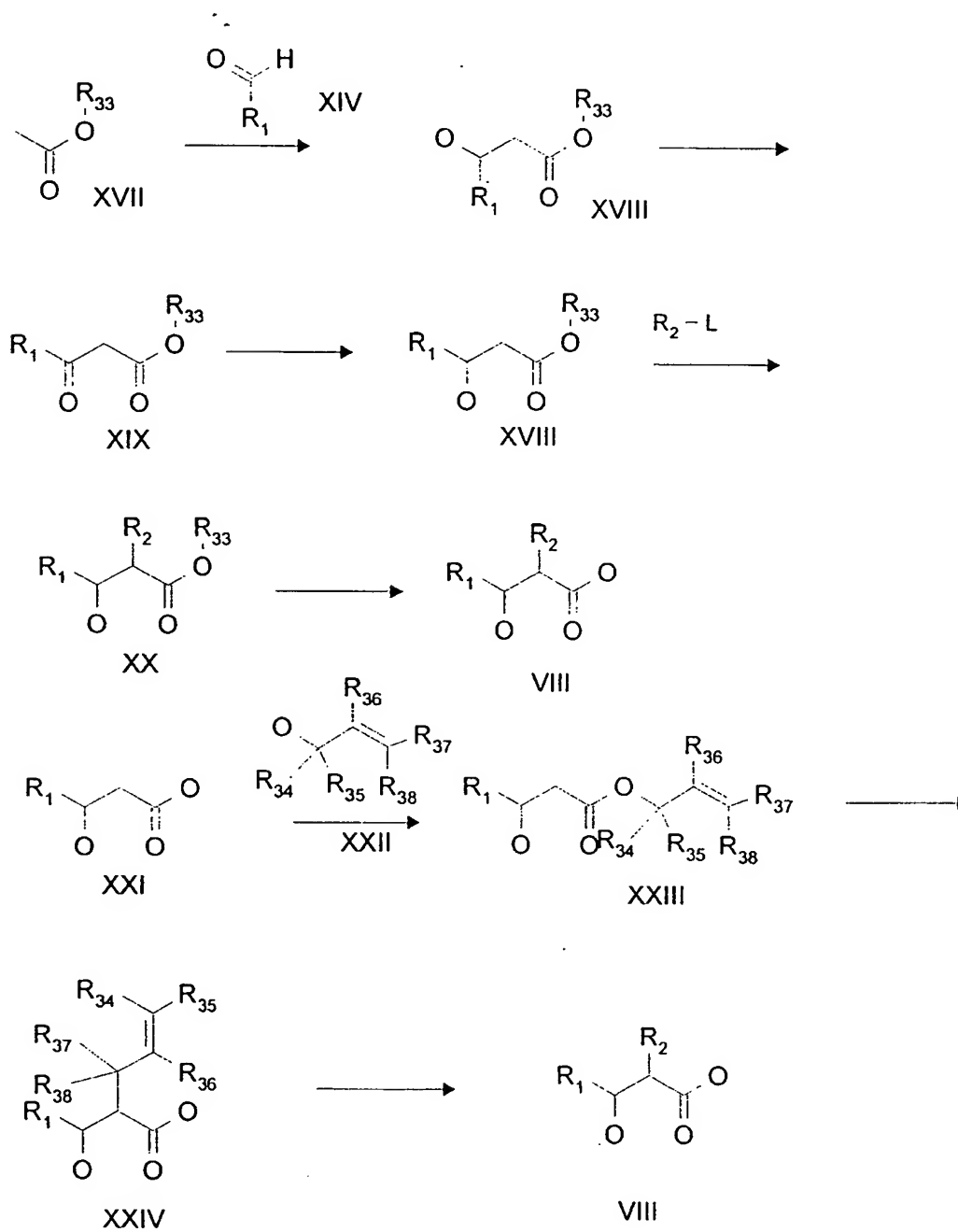
R₁ and R₂ are as defined as for formula (II).

R₃₂ is lower alkoxy or 1-oxazolidinyl.

- 5 A carbonyl compound of formula (XIII), where R₃₂ is an alkoxy group such as methoxy or tert-butoxy, may be treated with a strong base such as LDA in a solvent such as THF at a temperature of from -78 °C to 0 °C, followed by treatment with the aldehyde (XIV) to provide (XV). Where R₃₂ is a oxazolidinon-1-yl substituent, treatment of (XIII) with a Lewis acid such as di(n-butyl)boron
- 10 trifluoromethanesulfonate in the presence of N,N-diisopropylethylamine in a suitable solvent such as dichloromethane at a temperature of 0 °C, followed by addition of the aldehyde (XIV) provides (XV). Treatment of (XV) with aqueous base in the presence or absence of hydrogen peroxide affords (VIII) upon acidification. The acid (VIII) may be converted directly to (IX) as in reaction Scheme 2, or may be treated
- 15 with a dehydrating agent such a p-toluenesulfonyl chloride in pyridine or with triphenylphosphine and diethyl azodicarboxylate in a suitable solvent such as THF, to afford the lactone (XVI). Treatment of the lactone (XVI) with H₂NORPG₁ in the presence of a Lewis acid such as trimethylaluminum in a suitable solvent such as toluene affords the alcohol (IX).

Reaction Scheme 4 depicts the preparation of compounds of general formula (VIII).

Reaction Scheme 4



5

R_1 and R_2 are as defined for formula (II).

RPG₁ is as defined for reaction Scheme 1.

R₃₃ is lower alkyl.

L is bromide, iodide, or trifluoromethanesulfonyloxy.

R₃₄, R₃₅, R₃₆, R₃₇, and R₃₈ may be, independently, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, or hydrogen, where alkyl, alkenyl, alkynyl, and cycloalkyl substituents may contain one or more O, S, SO, or SO₂ substituents.

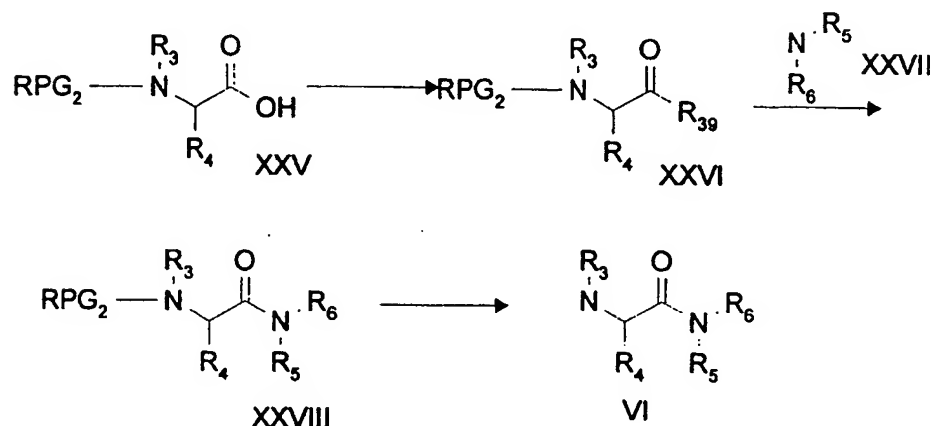
The ketoester of general formula (XIX), if not commercially available, may be prepared by reaction of ester (XVII) with a strong base such as LDA followed by treatment with the aldehyde (XIV). The resulting hydroxyester (XVIII) may be used directly or converted to the ketoester (XIX) by oxidation with, for example, pyridinium dichromate in a solvent such as dichloromethane. The ketoester of general formula (XIX) may be reduced with a reducing agent such as sodium borohydride to afford the hydroxyester (XVIII), where R₃₃ is a small alkyl group such as ethyl, methyl, or tert-butyl. Alternately, a chiral catalyst or chiral ligand in the presence of a reducing agent such as hydrogen or a metal hydride such as borane or LAH may be employed to afford (XVIII) with chiral induction at the newly formed asymmetric center. The alcohol (XVIII) may be converted to (XX) by treatment with a strong base such as LDA in a suitable solvent such as THF, followed by the addition of R₂-L in the presence or absence of a cosolvent such as DMPU. Removal of the ester group by hydrolysis with aqueous hydroxide ion or, in the case where R₃₃ is tert-butyl, by treatment with a strong acid such as TFA, affords (VIII). Hydroxy acid (XXI) is obtained by hydrolysis of the ester group of (XVIII) with aqueous alkali. (XXI) may be obtained by treatment of (XVIII) with TFA, where R₃₃ is tert-butyl. Coupling of the hydroxy acid (XXI) with an allylic alcohol (XXII) in the presence of a dehydrating agent such as EDC and a catalyst such as 4-dimethylaminopyridine provides the ester (XXIII). Alternately, protection of the alcohol functionality of ester (XVIII) with, for example, a tert-butyldimethylsilyl group, may be required before processing of (XVIII) to the acid. Hydrolysis of the ester as before with aqueous base followed by activation of the acid functionality as its acid chloride with oxalyl chloride and addition of the alcohol (XXII) in the presence of an organic base such as triethylamine provides the ester (XXIII) with the hydroxyl group protected. Deprotection of the hydroxyl group, if so protected, and treatment of the resulting ester (XXIII) with a strong base such as LDA in a solvent such as 1,2-dimethoxyethane at a temperature of -78 °C, followed by warming of the mixture to a temperature of between 0 °C and 90 °C, followed by acidification of the mixture provides the acid (XXIV). Reduction of the olefinic group in (XXIV) with hydrogen and a metal catalyst such as palladium on carbon provides the acid (VIII). Alternately, the olefin in compounds of general

formula (XXIV) may be left in place until a later stage and then saturated with, for example, hydrogen gas in the presence of palladium on carbon.

The preparation of compounds of general formula (VI) is shown in reaction Scheme 5.

5

Reaction Scheme 5



R_3 , R_4 , R_5 , and R_6 are as defined for general formula (II).

RPG_2 is a protecting group such as tert-butoxycarbonyl or benzyloxycarbonyl.

10 R_{39} is hydroxyl or halogen.

The acid of formula (XXV) may be converted *in situ* to (XXVI), where R_{39} is bromide, by treatment with bromo-tris(pyrrolidino)phosphonium hexafluorophosphate in a suitable solvent such as DMF in the presence of an organic base such as N, N-diisopropylethylamine. Addition of the amine (XXVII) in the displacement step in the presence of a suitable solvent such as DMF and an organic base such as N, N-diisopropylethylamine affords the amide (XXVIII). Alternatively, the intermediate of formula (XXVI) where R_{39} is hydroxyl may be treated with carbonyldiimidazole in a solvent such as dichloromethane, followed by treatment with the amine (XXVII) to afford (XXVIII). Alternatively, the intermediate of formula (XXV) may be treated with HOBt, the amine (XXVII), an organic base such as NMM, and a carbodiimide reagent such as EDC in a suitable solvent such as DMF, at a temperature of 0 °C to 80 °C to provide (XXVIII). The compound of formula (XXVIII) may be converted to (VI) by deprotection, conditions being particular to the nature of RPG_2 . For example, where RPG_2 is tert-butoxycarbonyl, conversion of (XXVIII) to (VI) may be accomplished by treatment of (XXVIII) with trifluoroacetic acid in the presence or

15

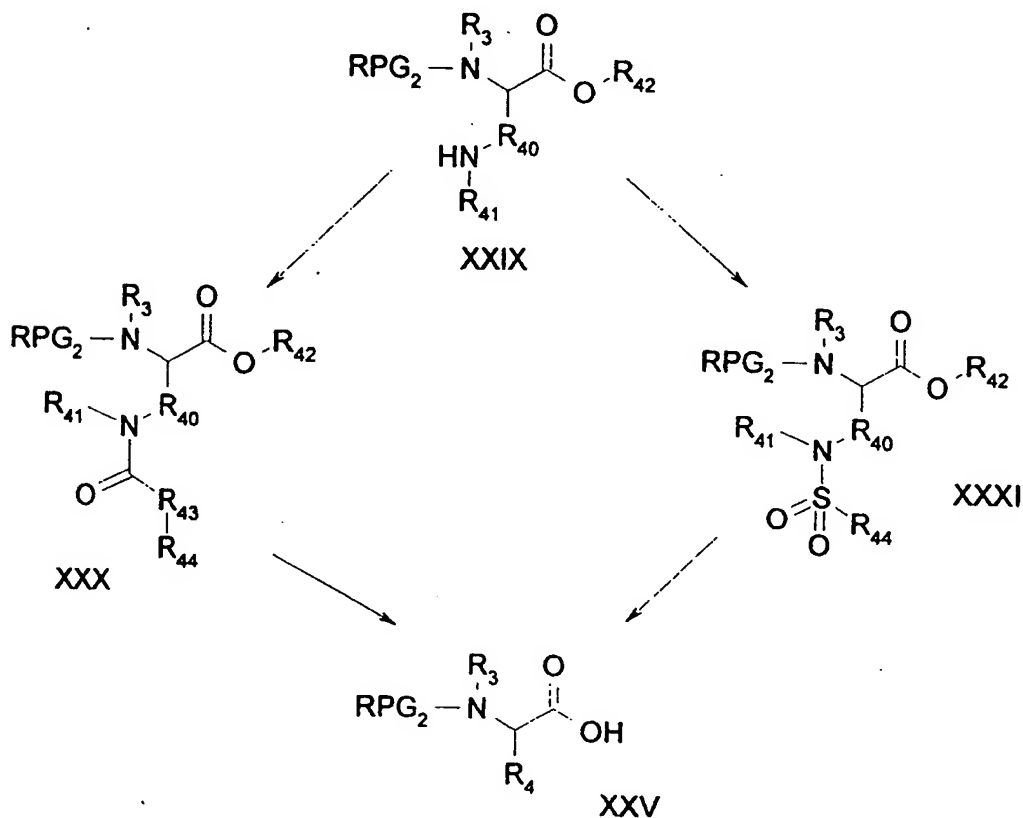
20

25

absence of a suitable solvent such as dichloromethane, at a temperature of 0 °C to 50 °C.

A preparation of compounds of general formula (XXV) is shown in reaction Scheme 6.

Reaction Scheme 6



5

R_3 and R_4 are as defined for general formula (II).

RPG_2 is a protecting group such as tert-butoxycarbonyl or benzyloxycarbonyl.

R_{40} is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, or heteroarylene, where alkylene, alkenylene, alkynylene, cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO_2 substituents.

R_{41} is lower alkyl or hydrogen.

R_{42} is lower alkyl or hydrogen.

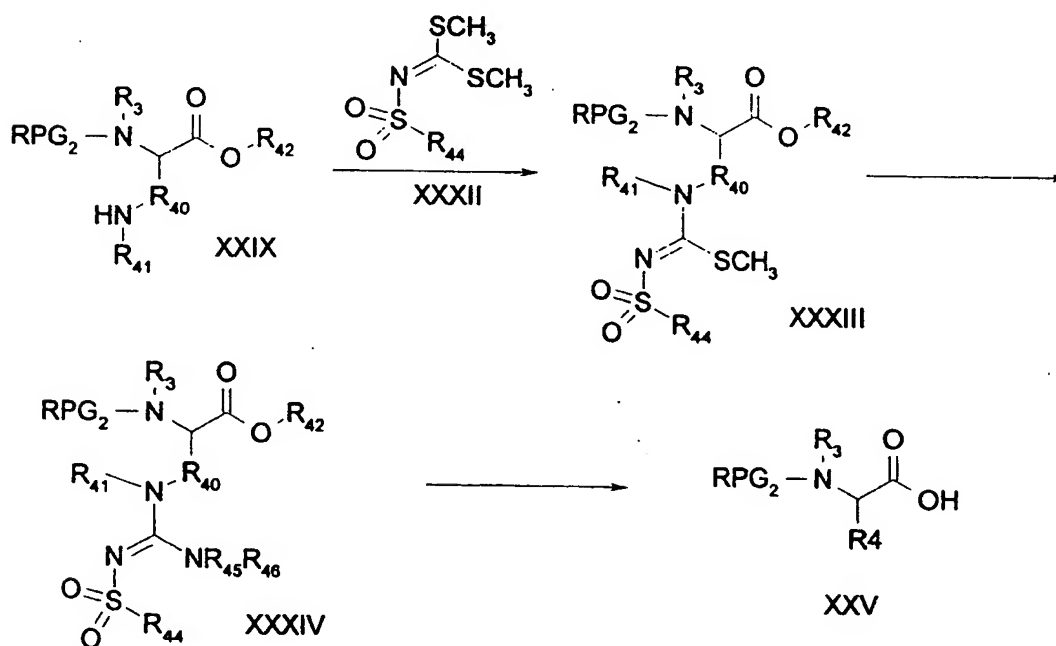
R_{43} is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, O, NH, N-alkyl, or heteroarylene, where alkylene, alkenylene, alkynylene, cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO_2 substituents.

15

R_{44} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO₂ substituents.

- The compound (XXIX) may be treated with the reagent R_{44} - R_{43} -COCl in a solvent such as dichloromethane in the presence of tertiary base such as triethylamine to afford (XXX). Alternately, (XXIX) may be treated with R_{44} - R_{43} -COOH (where R_{43} is not O, N, or N-alkyl) and a dehydrating agent such as EDC in a solvent such as DMF to afford (XXX). The compound (XXX) where R_{43} is NH may be prepared by treating (XXIX) with R_{44} -NCO in a solvent such as dichloromethane. (XXXI) may be prepared by treating (XXIX) with R_{44} -SO₂Cl in the presence of a tertiary amine base such as NMM in a solvent such as dichloromethane. Removal of the alkyl group R_{42} by saponification with aqueous base (or, if appropriate and where R_{42} is tert-butyl, by treatment with trifluoroacetic acid) provides (XXV).
- Reaction scheme 7 depicts an alternate preparation of an intermediate of general formula (XXV).

Reaction Scheme 7



- R_3 and R_4 are as defined for general formula (II).
 RPG_2 is a protecting group such as tert-butoxycarbonyl or benzyloxycarbonyl.

R₄₀ is is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, or heteroarylene, where alkylene, alkenylene, alkynylene, cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO₂ substituents.

5 R₄₁ is lower alkyl or hydrogen.

R₄₂ is lower alkyl or hydrogen.

R₄₄ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO₂ substituents.

10 R₄₅ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO₂ substituents.

R₄₆ is is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl

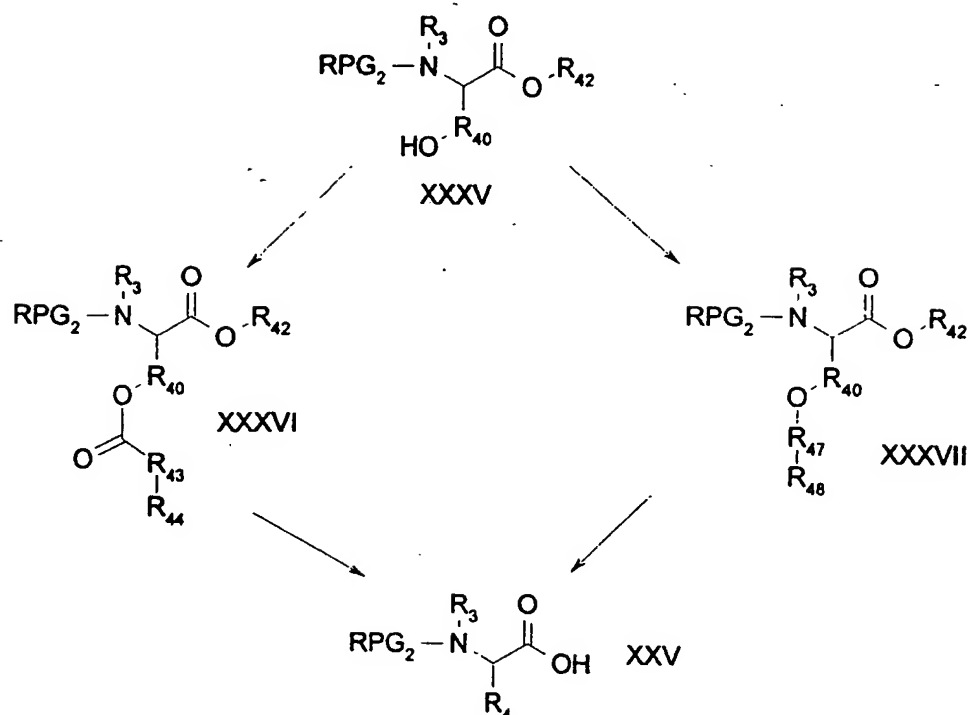
15 substituents may contain one or more O, S, SO, or SO₂ substituents.

R₄₅ and R₄₆ may be taken together to constitute three- to ten-membered ring.

The amine compound (XXIX) is treated with (XXXII) in the presence of a tertiary base such as triethylamine or NMM to afford (XXXIII). Treatment of (XXXIII) with silver nitrate and an amine HNR₄₅R₄₆ provides (XXXIV). Removal
20 of the alkyl group R₄₂ by saponification with aqueous base (or, if appropriate and where R₄₂ is tert-butyl, by treatment with trifluoroacetic acid) provides (XXV).

Reaction scheme 8 depicts an alternate preparation of an intermediate of general formula (XXV).

Reaction Scheme 8



R_3 and R_4 are as defined for general formula (II).

RPG_2 is a protecting group such as tert-butoxycarbonyl or benzyloxycarbonyl.

R_{40} is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, or heteroarylene, where alkylene, alkenylene, alkynylene, cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO_2 substituents.

R_{42} is lower alkyl or hydrogen.

R_{43} is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, O, NH, N-alkyl, or heteroarylene, where alkylene, alkenylene, alkynylene, cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO_2 substituents.

R_{44} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO_2 substituents.

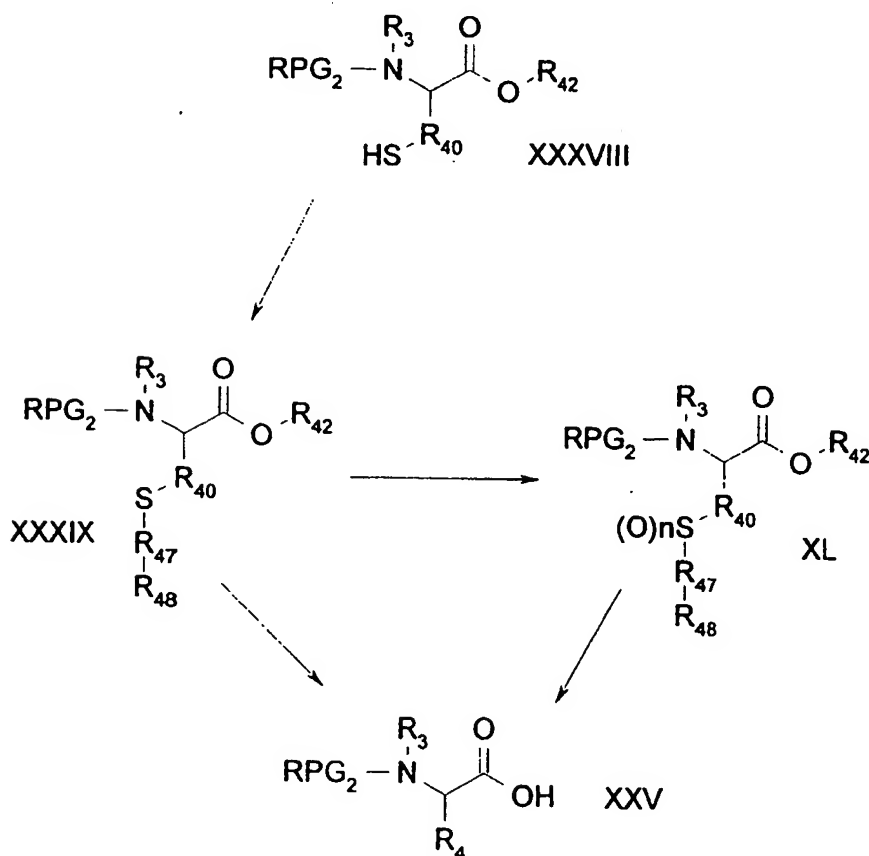
R_{47} is alkylene or heteroarylene.

R_{48} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO_2 substituents.

- The hydroxy compound (XXXV) may be treated with the reagent R_{44} - R_{43} -COCl in a solvent such as dichloromethane in the presence of tertiary base such as triethylamine to afford (XXXVI). Alternately, (XXXV) may be treated with R_{44} - R_{43} -COOH (where R_{43} is not O, N, or N-alkyl) and a dehydrating agent such as EDC and a catalyst such as DMAP in a solvent such as DMF or dichloromethane to afford (XXXVI). The compound (XXXVI) where R_{43} is NH may be prepared by treating (XXXV) with R_{44} -NCO in a solvent such as dichloromethane. The ether (XXXVII) may be prepared by treating (XXXV) with R_{48} R_{47} Br or R_{48} R_{47} I in the presence of a base such as potassium carbonate or sodium hydride in a solvent such as DMF. .
- Removal of the alkyl group R_{42} by saponification with aqueous base (or, if appropriate and where R_{42} is tert-butyl, by treatment with trifluoroacetic acid) provides the acid (XXV).

Reaction scheme 9 depicts an alternate preparation of an intermediate of general formula (XXV).

Reaction Scheme 9



R_3 and R_4 are as defined for general formula (II).

RPG₂ is a protecting group such as tert-butoxycarbonyl or benzyloxycarbonyl.

R₄₀ is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, or heteroarylene, where alkylene, alkenylene, alkynylene, cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO₂ substituents.

R₄₂ is lower alkyl or hydrogen.

R₄₇ is alkylene or heteroarylene.

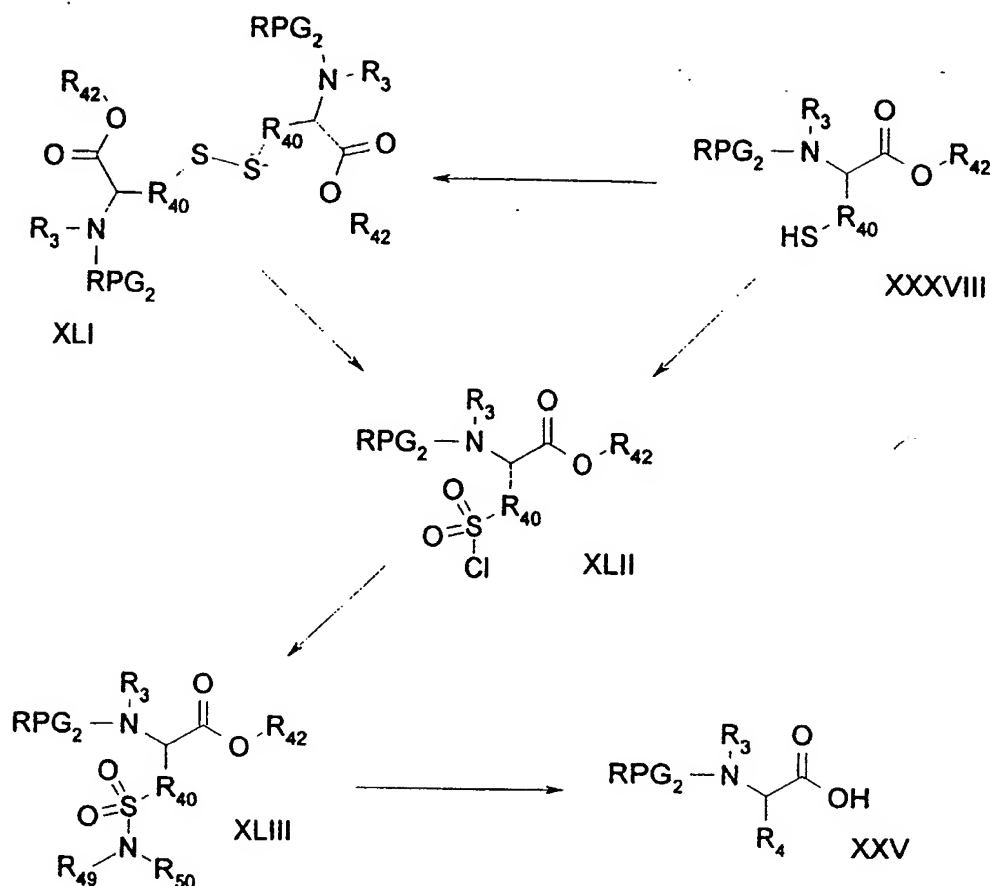
R₄₈ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO₂ substituents.

n is 1 to 2.

The thioether (XXXIX) may be prepared by treating (XXXVIII) with R₄₈R₄₇Br or R₄₈R₄₇I and a base such as potassium carbonate or sodium hydride in a solvent such as DMF. The sulfur atom may be oxidized with a reagent such as m-chloroperoxybenzoic acid. Use of one molar equivalent of oxidant may be employed to provide (XL) where n is 1. Use of two molar equivalents of oxidant may be employed to provide (XL) where n is 2. Removal of the alkyl group R₄₂ in either (XL) or (XXXIX) by saponification with aqueous base (or, if appropriate and where R₄₂ is tert-butyl, by treatment with trifluoroacetic acid) provides the acid (XXV).

Reaction scheme 10 depicts an alternate preparation of an intermediate of general formula (XXV).

Reaction Scheme 10



R_3 and R_4 are as defined for general formula (II).

RPG_2 is a protecting group such as tert-butoxycarbonyl or benzyloxycarbonyl.

R_{40} is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, or heteroarylene, where alkylene, alkenylene, alkynylene, cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO_2 substituents.

R_{42} is lower alkyl or hydrogen.

R_{49} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO_2 substituents.

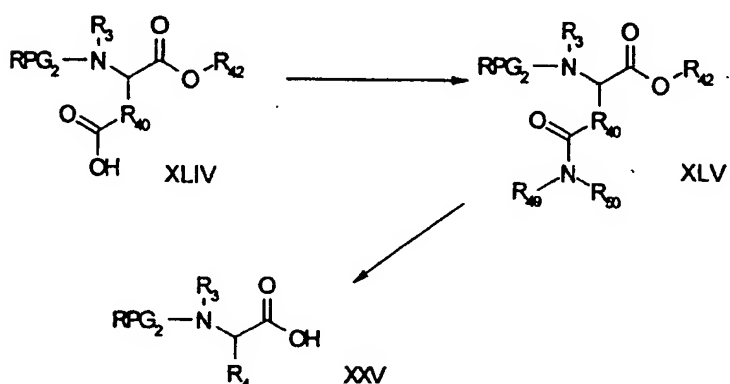
R_{50} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO_2 substituents.

R_{49} and R_{50} may be taken together to constitute a three- to ten-membered ring.

The thiol (XXXVIII) may be oxidized to the disulfide (XLI) by treatment with a mild base such as TEA and oxygen or air. Either the thiol (XXXVIII) or the disulfide (XLI) may be converted to the sulfonyl chloride (XLII) by treatment with chlorine gas in tetrachloromethane. Treatment of the sulfonyl chloride (XLII) with an amine $R_{49}R_{50}NH$ in the presence of a tertiary amine base such as TEA or NMM affords (XLIII). Removal of the alkyl group R_{42} in (XLIII) by saponification with aqueous base (or, if appropriate and where R_{42} is tert-butyl, by treatment with trifluoroacetic acid) provides the acid (XXV).

Reaction scheme 11 depicts an alternate preparation of an intermediate of general formula (XXV).

Reaction Scheme 11



R_3 and R_4 are as defined for general formula (II).

RPG_2 is a protecting group such as tert-butoxycarbonyl or benzyloxycarbonyl.

R_{40} is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, or heteroarylene, where alkylene, alkenylene, alkynylene, cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO_2 substituents.

R_{42} is lower alkyl or hydrogen.

R_{49} is is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO_2 substituents.

R_{50} is is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents may contain one or more O, S, SO, or SO_2 substituents.

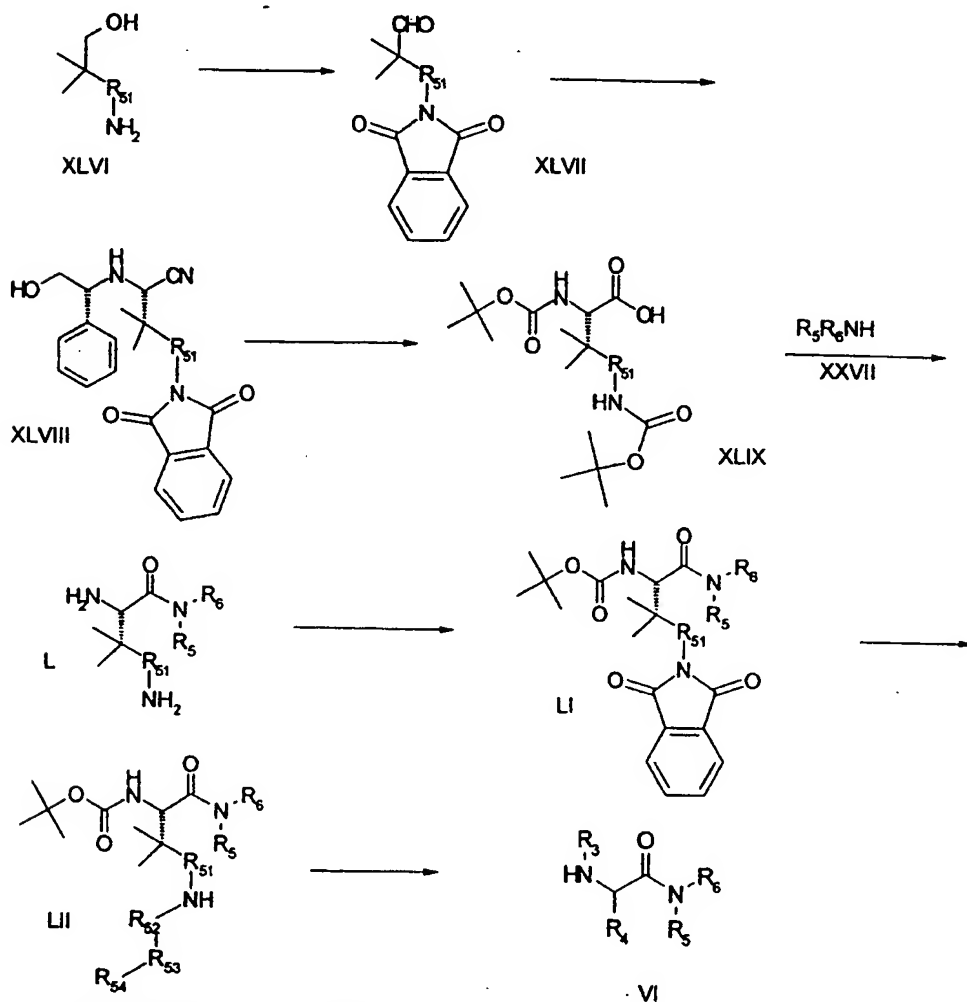
R_{49} and R_{50} may be taken together to constitute a three- to ten-membered ring.

The acid (XLIV) may be converted to the amide (XLV) by treatment of (XLIV) and the amine $R_{49}R_{50}NH$ with a dehydrating agent such as EDC or BOP in the presence of HOBT. Removal of the alkyl group R_{42} in (XLV) by saponification with

aqueous base (or, if appropriate and where R_{42} is tert-butyl, by treatment with trifluoroacetic acid) provides the acid (XXV).

Reaction scheme 12 depicts an alternate preparation of an intermediate of general formula (VI).

Reaction Scheme 12



R_3 , R_4 , R_5 , and R_6 are as defined for general formula (II).

R_{51} is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, or heteroarylene, where alkylene, alkenylene, alkynylene, cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO_2 substituents.

R_{52} is CO or SO_2 .

R_{53} is NH, N-alkyl, alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, arylene, or heteroarylene, where alkylene, alkenylene, alkynylene,

cycloalkylene, and cycloalkenylene substituents may contain one or more O, S, SO, or SO₂ substituents.

R₅₄ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, or hydrogen, where alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl substituents
5 may contain one or more O, S, SO, or SO₂ substituents.

The amino alcohol (XLVI) is treated with phthalic anhydride in a solvent such as toluene at a temperature of from 25 °C to 120 °C, or with N-ethoxycarbonylphthalimide and sodium bicarbonate at a temperature of from -20 °C to 45 °C, followed by oxidation of the resulting phthalimido alcohol with an
10 oxidizing agent such as pyridinium chlorochromate to provide the aldehyde (XLVII). Treatment of (XLVII) with (R)-phenylglycinol in a solvent system such as chloroform - MeOH followed by addition of trimethylsilyl cyanide affords (XLVIII) with stereochemistry as depicted. Treatment of (XLVIII) with 12 N HCl at a temperature of 25 °C to 70 °C is followed by treatment with hydrazine and acidification with 1 N
15 HCl. The product is treated in a solvent such as MeOH with palladium hydroxide on carbon under 60 psi of hydrogen pressure at a temperature of from 25 °C to 80 °C, followed by treatment with di-tert-butyl dicarbonate and aqueous sodium hydroxide to afford (XLIX) after acidification. Treatment of (XLIX) with the amine (XXVII) and a dehydrating agent such as EDC in the presence of HOBt in a solvent such as DMF
20 at a temperature of 0 °C to 25 °C, followed by treatment with HCl in a solvent such as dichloromethane or dioxane affords (L). Treatment of (L) with N-ethoxycarbonylphthalimide in a solvent such as DMF with TEA at a temperature of -20 °C, followed by treatment of the product with di-tert-butyl dicarbonate and DMAP in a solvent such as dichloromethane affords (LI). (LI) may be treated with hydrazine
25 in a solvent such as MeOH or ethanol, and the resulting amine may be treated with R₅₄R₅₃R₅₂Cl to provide (LII) where R₅₃ is not NH. Use of R₅₄NCO in this step provides (LII) where R₅₂ is CO and R₅₃ is NH. Treatment of (LII) with HCl in dioxane or trifluoroacetic acid affords (VI).

30 PHARMACEUTICAL FORMULATION AND DOSES

The compounds of the present invention can be administered in such oral (including buccal and sublingual) dosage forms as tablets, capsules (each including
timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Likewise, they may also be
35 administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular inhalation or

insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.1 to 300 mg/kg of body weight per day, and particularly 1 to 100 mg/kg of body weight per day. Oral dosage units will generally be administered in the range of from 1 to about 250 mg and more preferably from about 25 to 250 mg. The daily dosage for a 70 kg mammal will generally be in the range of about 10 mg to 5 grams of a compound of formula I or II.

While the dosage to be administered is based on the usual conditions such as the physical condition of the patient, age, body weight, past medical history, route of administrations, severity of the conditions and the like, it is generally preferred for oral administration to administer to a human. In some cases, a lower dose is sufficient and, in some cases, a higher dose or more doses may be necessary. Topical application similarly may be once or more than once per day depending upon the usual medical considerations. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically

acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginat, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or

polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound.

5 Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or
10 saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

15 The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of
20 monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with
25 palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphoteric block copolymers of hydrogels.

30 The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, more particularly, 0.5 to 90% of a compound of the formula (II) in combination with a pharmaceutically acceptable carrier.

Parenteral administration can be effected by utilizing liquid dosage unit forms such as sterile solutions and suspensions intended for subcutaneous, intramuscular or
35 intravenous injection. These are prepared by suspending or dissolving a measured amount of the compound in a non-toxic liquid vehicle suitable for injection such as aqueous oleaginous medium and sterilizing the suspension or solution.

Alternatively, a measured amount of the compound is placed in a vial and the vial and its contents are sterilized and sealed. An accompanying vial or vehicle can be provided for mixing prior to administration. Non-toxic salts and salt solutions can be added to render the injection isotonic. Stabilizers, preservations and emulsifiers can
5 also be added.

Rectal administration can be effected utilizing suppositories in which the compound is admixed with low-melting water-soluble or insoluble solids such as polyethylene glycol, cocoa butter, higher ester as for example flavored aqueous solution, while elixirs are prepared through myristyl palmitate or mixtures thereof.

10 Topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may also contain compatible conventional
15 carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized
20 packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an
25 inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The preferred pharmaceutical compositions are those in a form suitable for oral administration, such as tablets and liquids and the like and topical formulations.

According to the present invention there is provided a pharmaceutical
30 composition comprising a pharmaceutically acceptable carrier and a pharmacologically effective amount of a compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof.

In preferred compositions the pharmacologically effective amount of a
35 compound of formula (II) as defined above or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof is sufficient to inhibit the cellular release of mature tumor necrosis factor

alpha, to inhibit a matrix metalloprotease, to inhibit the shedding of cell surface protein ectodomains, to inhibit the growth of tumor metastases, to treat diabetes or to treat arthritis.

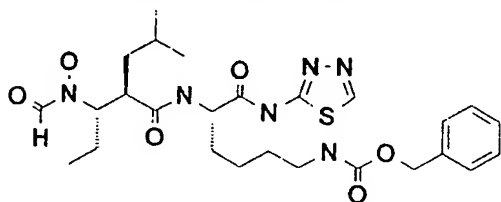
5

EXAMPLES

The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature. All compounds illustrated in the tables, above, were synthesized following one or more of the general synthesis schemes previously set forth. The following selected synthesis descriptions give detailed instruction on the practice of the general synthesis schemes, and one of ordinary skill in the art will readily be able to adapt one or more of the general synthesis schemes to an analogous synthesis, using details of the selected synthesis descriptions as guides, in the synthesis of compounds of the invention.

15

Example 1; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1*S*)-5-Benzoyloxycarbonylamino)-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide



20

Example 1a; Ethyl (3*R*)-3-Hydroxyhexanoate and Methyl (3*R*)-3-Hydroxyhexanoate

Ethyl butyrylacetate (50.0 g, 316 mmol) is stirred in 75 mL of absolute ethanol as [RuCl₂(BINAP)]₂•NEt₃ (0.139 g, 0.158 mmol) is added along with 2 N hydrochloric acid (0.158 mL, 0.316 mmol). The mixture is placed on a pressure hydrogenation apparatus and degassed by evacuating and filling with nitrogen several times. The vessel is then pressurized with hydrogen to 65 psi. The reaction is heated to 70 °C for 36 h and then is allowed to cool to 25 °C. The resulting reddish brown solution is concentrated under reduced pressure and the product distilled (40-50 °C, 200 millitorr) to give a clear oil (50.0 g, 99% yield, >99% enantiomeric excess determined by chiral analytical HPLC).

30

¹H NMR (400 MHz, CDCl₃) δ 4.17 (q, 2H), 4.01 (m, 1H), 2.95 (d, 1H), 2.47 (dd, 1H), 2.40 (dd, 1H), 1.58-1.38 (m, 4H), 1.38 (t, 3H), 0.94 (t, 3H) ppm.

Methyl (3*R*)-3-hydroxyhexanoate is prepared in the same manner described above in MeOH employing methyl butyrylacetate as the starting ketoester. The enantiomeric excess is 99% as determined by chiral analytical HPLC methods.

- 5 ¹H NMR (300 MHz, CDCl₃) δ 4.04 (m, 1H), 3.72 (s, 3H), 2.87 (d, 1H), 2.50 (dd, 1H), 2.46 (dd, 1H), 1.58-1.38 (m, 4H), 0.94 (t, 3H) ppm.

Example 1b; Methyl (2*R*,3*R*)-2-(2-Methyl-2-propene-1-yl)-3-hydroxypentanoate

- 10 To a solution of diisopropylamine (6.74 g, 66.7 mmol) in THF (60 mL) cooled to 0 °C is added n-butyllithium (66.7 mmol, 2.5 M in hexanes) and the resulting solution is stirred at 0 °C for 0.5 h. The reaction mixture is cooled to -50 °C followed by slow addition of methyl (3*R*)-3-hydroxypentanoate (prepared from methyl propionylacetate according to the procedure in example 1a) (4.0 g, 30.3 mmol), which
15 is then stirred for 0.5 h. Methallyl bromide (6.14 g, 45.5 mmol) and HMPA (5 mL) are added and the reaction mixture is allowed to warm to -20 °C and stirred for 16 h. The reaction mixture is quenched by addition of a saturated ammonium chloride solution (5 mL), poured into 1 N hydrochloric acid (50 mL) and extracted with two
20 100 - mL portions of EtOAc. The organic layer is dried over magnesium sulfate, concentrated, and then purified by silica gel chromatography (3:1 hexanes - EtOAc) to afford methyl (2*R*,3*R*)-2-(2-methyl-2-propene-1-yl)-3-hydroxypentanoate as a yellow oil (3.85 g, 68% yield).
¹H NMR (300 MHz, CDCl₃) δ 4.80 (d, 2H), 3.76 (s, 3H), 3.62 (m, 1H), 2.74 (m, 1H), 2.54 (m, 2H), 2.36 (m, 1H), 1.88 (s, 3H), 1.62-1.48 (m, 2H), 1.26 (m, 1H), 1.04 (t,
25 3H) ppm.
ESI-MS m/z 187 (M+ H)⁺.

Example 1c; Methyl (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxypentanoate

- 30 A solution of methyl (2*R*,3*R*)-2-(2-methyl-2-propene-1-yl)-3-hydroxypentanoate (3.85 g, 20.7 mmol) in EtOAc (30 mL) is treated with 10% palladium on carbon (300 mg). The resulting suspension is repeatedly evacuated and purged with hydrogen, then stirred under 1 atmosphere pressure of hydrogen gas for 36 h. The catalyst is filtered and the filtrate is concentrated *in vacuo* to provide
35 methyl (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxypentanoate as an oil (3.61 g, 93% yield).

¹H NMR (300 MHz, CDCl₃) δ 3.76 (s, 3H), 3.56 (m, 1H), 2.62 (dt, 1H), 2.42 (bd, 1H), 1.80-1.41 (m, 5H), 1.04 (t, 3H), 0.96 (dd, 6H) ppm.

Example 1d; (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxypentanoic Acid

5

To a solution of methyl (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxypentanoate (3.6 g, 19.15 mmol) in THF - MeOH (3:1, 80 mL) is added 1 N aqueous sodium hydroxide (21.06 mmol). The solution is stirred at 23 °C for 20 h, then is acidified to pH 3 with 1 N hydrochloric acid and extracted with two 100 - mL portions of EtOAc. The combined organic solutions are dried over anhydrous magnesium sulfate and concentrated *in vacuo* to provide (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxypentanoic acid as an oil (3.33 g, 100% yield).

10

¹H NMR (300 MHz, CDCl₃) δ 3.62 (m, 1H), 2.62 (dt, 1H), 2.42 (bd, 1H), 1.80-1.40 (m, 5H), 1.04 (t, 3H), 0.96 (dd, 6H) ppm.

15

APCI-MS *m/z* 173 (M-H)⁺.

Example 1e; (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxypentanoic Acid 2-Tetrahydropyranyloxyamide

20

To a solution of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxypentanoic acid (3.33 g, 19.15 mmol) in dichloromethane (20 mL) is added O-(2-tetrahydropyranyl) hydroxylamine (4.48 g, 38.3 mmol) and EDC (4.41 g, 23.0 mmol). The resulting solution is stirred at 23 °C for 3 h, then concentrated and diluted with EtOAc (150 mL). The organic layer is washed sequentially with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. The crude product is concentrated and purified by silica gel chromatography (3:1 EtOAc - hexanes) to provide (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxypentanoic acid 2-tetrahydropyranyloxyamide as a foam (4.10 g, 78% yield).

25

30

¹H NMR (300 MHz, CDCl₃) δ 8.78 (d, 1H), 5.02 (m, 1H), 4.02 (m, 1H), 3.62 (m, 2H), 2.94 (m, 1H), 2.24 (m, 1H), 1.94-1.48 (m, 10H), 1.42 (m, 1H), 1.04 (t, 3H), 0.96 (m, 6H) ppm.

APCI-MS *m/z* 272 (M-H)⁺.

35

Example 1f; (3*R*,4*S*) 3-(2-Methyl-1-propyl)-4-ethyl-1-(2-tetrahydropyranyloxy)azetidin-2-one

To a solution of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxypentanoic acid 2-tetrahydropyranyloxyamide (4.1 g, 15.02 mmol) in dichloromethane (15 mL) at 0 °C is added pyridine (5 mL) and methanesulfonyl chloride (1.89 g, 16.5 mmol). The resulting solution is allowed to warm to 23 °C and stirred for 18 h, then concentrated and diluted with EtOAc (100 mL). The organic layer is washed with 1 N hydrochloric acid, saturated aqueous cupric sulfate, and is dried over anhydrous magnesium sulfate and concentrated to provide the desired methanesulfonate intermediate.

A suspension of potassium carbonate (6.22 g) in acetone (120 mL) is heated to reflux for 1 h. A solution of the above methanesulfonate in acetone (30 mL) is added and the resulting suspension is heated to reflux for 16 h. The reaction mixture is filtered, concentrated, and the crude product is purified by silica gel chromatography (2:1 hexanes - EtOAc) to provide (3*R*,4*S*)-3-(2-methyl-1-propyl)-4-ethyl-1-(2-tetrahydropyranyloxy)azetidin-2-one as an oil (3.34 g, 87% yield).
¹H NMR (300 MHz, CDCl₃) δ 5.22 and 5.04 (two bs, 1H), 4.24 and 4.16 (two dt, 1H), 3.86 and 3.82 (two q, 1H), 3.66 (m, 1H), 3.16 (m, 1H), 1.96-1.62 (m, 10H), 1.41 (m, 1H), 1.04 and 1.02 (two t, 3H), 0.96 (d, 6H) ppm.
ESI-MS *m/z* 278 (M+Na)⁺.

Example 1g; (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoic Acid

To a solution of (3*R*,4*S*)-3-(2-methyl-1-propyl)-4-ethyl-1-(2-tetrahydropyranyloxy)azetidin-2-one (3.34 g, 13.1 mmol) in THF - MeOH (2:1, 45 mL) is added 1 N aqueous sodium hydroxide (15 mL). The solution is stirred at 23 °C for 36 h, then acidified to pH 3 with saturated sodium bisulfate and extracted with EtOAc (2 x 100 mL). The organic layer is dried over anhydrous sodium sulfate and concentrated to provide (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoic acid as an oil (3.0 g, 84% yield).
¹H NMR (300 MHz, CDCl₃) δ 4.88 and 4.80 (two m, 1H), 4.06 and 3.94 (two m, 1H), 3.62 (m, 1H), 3.14 (m, 1H), 3.04 and 2.92 (dt and m, 1H) 1.96-1.44 (m, 10H), 1.22 (m, 1H), 1.04 and 1.02 (two t, 3H), 0.96 (m, 6H) ppm.
APCI-MS *m/z* 274 (M+ H)⁺.

Example 1h; Pentafluorophenyl (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoate

To a solution of (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoic acid (3.0 g, 10.99 mmol) in pyridine (10 mL) at 0 °C is added formic acetic anhydride (2.5 mL). The resulting solution is stirred at 0 °C for 5 h, concentrated, then diluted with EtOAc (11 mL). To the solution of crude acid is added pentafluorophenol (2.12 g, 11.54 mmol), *N*-methyl morpholine (1.17 g, 11.54 mmol) and dicyclohexylcarbodiimide (2.38 g, 11.54 mmol). The resulting solution is stirred at 23 °C for 20 h, then is filtered. The filtrate is washed with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The organic layer is dried over anhydrous magnesium sulfate, concentrated, and purified by silica gel chromatography (8:1 hexanes - EtOAc) to provide pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoate as an oil (3.61 g, 70% yield).
¹H NMR (400 MHz, CDCl₃) δ 8.62 and 8.02 (two d, 1H), 5.04 and 4.84 (two m, 1H), 4.62 and 3.58 (two m, 1H), 4.02 (m, 1H), 3.64 (m, 1H), 3.24 and 3.06 (two dt, 1H), 2.02-1.36 (m, 11H), 0.96 (m, 9H) ppm.
APCI-MS *m/z* 490 (M+Na)⁺.

Example 1i; (2*S*)-6-Benzylloxycarbonylamino-2-*tert*-butoxycarbonylamino-hexanoic Acid 1,3,4-Thiadiazol-2-ylamide

To a solution of (2*S*)-6-benzylloxycarbonylamino-2-*tert*-butoxycarbonylamino-hexanoic acid (1.09 g, 2.87 mmol) in dichloromethane (5 mL) is added 1,1-carbonyldiimidazole (0.47 g, 2.87 mmol). The resulting solution is stirred for 1 h, then 2-amino-1,3,4-thiadiazole (0.29 g, 2.87 mmol) is added and the reaction stirred for an additional 18 h. The mixture is diluted with dichloromethane (60 mL) and washed with 1 M aqueous sodium carbonate. The organic layer is dried over anhydrous magnesium sulfate, concentrated, and purified by silica gel chromatography (1:1 EtOAc - hexanes) to provide (2*S*)-6-benzylloxycarbonylamino-2-*tert*-butoxycarbonylamino-hexanoic acid 1,3,4-thiadiazol-2-ylamide as a foam (0.81 g, 61% yield).
¹H NMR (300 MHz, CDCl₃) δ 13.35 (bs, 1H), 8.78 (bs, 1H), 7.32 (m, 5H), 6.56 (m, 1H), 5.09 (m, 3H), 4.46 (m, 1H), 3.21 (m, 2H), 2.91 (m, 2H), 1.95-1.56 (m, 4H), 1.26 (s, 9H) ppm.
APCI-MS *m/z* 464 (M+H)⁺.

Example 1j; (2*S*)-6-Benzylloxycarbonylamino-2-amino-hexanoic Acid 1,3,4-Thiadiazol-2-ylamide

To a solution of (2*S*)-6-benzyloxycarbonylamino-2-tert-butoxycarbonylaminohexanoic acid 1,3,4-thiadiazol-2-ylamide (0.81 g, 1.75 mmol) in dichloromethane (8 mL) is added trifluoroacetic acid (2 mL). The resulting solution is stirred for 4 h, concentrated, diluted with EtOAc (50 mL) and washed with 1 N aqueous sodium hydroxide. The organic layer is dried over anhydrous sodium sulfate and concentrated to provide (2*S*)-6-benzyloxycarbonylamino-2-aminohexanoic acid 1,3,4-thiadiazol-2-ylamide as a solid (0.62 g, 98% yield).
¹H NMR (300 MHz, CDCl₃) δ 8.82 (s, 1H), 7.31 (m, 5H), 5.42 (bs, 1H), 5.04 (s, 2H), 3.64 (m, 1H), 3.16 (m, 4H), 1.85 (m, 1H), 1.62 (m, 1H), 1.51 (m, 4H) ppm.
APCI-MS m/z 364 (M+H)⁺.

Example 1k; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1*S*)-5-Benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide

To a solution of pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoate (70 mg, 0.15 mmol) in DMF (1 mL) is added (2*S*)-6-benzyloxycarbonylamino-2-aminohexanoic acid 1,3,4-thiadiazol-2-ylamide (65 mg, 0.18 mmol), N-methylmorpholine (15 mg, 0.15 mmol) and HOBT (2 mg, 0.015 mmol). The resulting solution is heated to 50 °C and stirred for 24 h then poured into 1 M aqueous sodium carbonate and extracted with 20 mL of 1:1 EtOAc - hexanes. The organic layer is dried over anhydrous magnesium sulfate, concentrated, and purified by silica gel chromatography (1:1 EtOAc - hexanes) to provide (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide as a foam (60 mg, 62% yield).
¹H NMR (300 MHz, CDCl₃) δ 8.62 and 8.02 (two d, 1H), 5.04 and 4.84 (two m, 1H), 4.42 and 3.58 (two m, 1H), 4.02 (m, 1H), 3.64 (m, 1H), 3.24 and 3.06 (two dt, 1H), 2.02-1.36 (m, 11H), 0.96 (m, 9H) ppm.
APCI-MS m/z 669 (M+H)⁺.

Example 1; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1*S*)-5-Benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide

A solution of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide (60 mg, 0.093 mmol) in acetic acid - water (4:1 v/v, 1

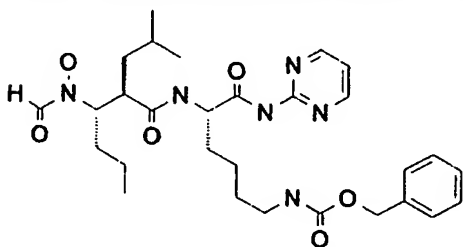
mL) is heated to 50 °C for 18 h. The reaction mixture is concentrated, then twice dissolved in toluene and concentrated. The crude product is recrystallized from dichloromethane - MeOH - ether to provide (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide as an off-white solid (41 mg, 79% yield).

¹H NMR (400 MHz, CD₃OD) δ 9.02 (s, 1H), 8.41 and 7.94 (two s, 1H), 7.3-7.22 (m, 5H), 5.06 (m, 2H), 4.56 (dd, 1H), 4.24 and 3.45 (two dt, 1H), 3.12 (t, 2H), 2.84 and 2.78 (two m, 1H), 1.82 (m, 3H), 1.58-1.40 (m, 7H), 1.16 (m, 1H), 0.95 (m, 3H), 0.92 (m, 6H) ppm.

APCI-MS *m/z* 585 (M+Na)⁺.

Anal. Calcd. for C₂₆H₃₈N₆O₆S · 0.5 H₂O: C, 54.62; H, 6.87; N, 14.70. Found: C, 54.70; H, 6.72; N, 14.41.

Example 2; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1*S*)-5-Benzyloxycarbonylamino-1-(1,3-pyrimidin-2-ylcarbamoyl)-1-pentyl]amide



Example 2a; Methyl (2*R*,3*R*)-2-(2-Methyl-2-propene-1-yl)-3-hydroxyhexanoate

To a stirred solution of diisopropylamine (19.4 mL, 139 mmol) in 70 mL of THF at -78 °C is added dropwise 86.6 mL (139 mmol) of 1.6 M *n*-butyllithium in hexanes over 15 min.. After 1 h, a solution of methyl (3*R*)-3-hydroxyhexanoate (9.2 g, 63 mmol) in 10 mL of THF is added dropwise over several minutes. The reaction mixture is stirred 1 h, then treated with a solution of 3-bromo-2-methyl-1-propene (7.6 mL, 75.6 mmol) in 10 mL of HMPA and is allowed to stand at -20 °C overnight. The reaction mixture is poured into ice-cold 1 N hydrochloric acid (300 mL) and extracted with two 200 - mL portions of EtOAc. The combined organic layers are washed with two 100 - mL portions of saturated aqueous sodium chloride, dried over sodium sulfate, and filtered. The solvents are removed under reduced pressure. Purification by flash chromatography on silica gel eluting with 10% EtOAc - hexanes affords 7 g (55%) of methyl (2*R*,3*R*)-2-(2-methyl-2-propene-1-yl)-3-hydroxyhexanoate as a colorless oil.

TLC *R_f* (hexanes - EtOAc, 1:1) 0.75.

¹H NMR (300 MHz, CDCl₃) δ 4.82 (s, 1H), 4.75 (s, 1H), 3.70 (s, 3H), 3.68 (m, 1H), 2.70 (m, 1H), 2.50 (m, 1H), 2.35 (dd, 1H), 1.75 (s, 3H), 1.60-1.65 (m, 4H), 0.95 (t, 3H) ppm.

5 Example 2b; Methyl (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxyhexanoate

A mixture of methyl (2*R*,3*R*)-2-(2-methyl-2-propene-1-yl)-3-hydroxyhexanoate (7 g, 34.6 mmol) and 1.7 g of 5% palladium on carbon (50 wt. % water content) in 50 mL of MeOH is stirred overnight under hydrogen gas at 1
10 atmosphere pressure. Filtration and concentration of the filtrate under reduced pressure affords 6.5 g (93%) of methyl (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxyhexanoate as a colorless oil.
TLC R_f (hexanes - EtOAc, 1:1) 0.75.
¹H NMR (300 MHz, CDCl₃) δ 3.75 (s, 3H), 3.65 (m, 1H), 2.57 (m, 1H), 2.10 (bs, 1H),
15 1.80-1.23 (m, 7H), 0.90 (m, 9H) ppm.

Example 2c; (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxyhexanoic Acid

A solution of methyl (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxyhexanoate (6.5
20 g, 31.9 mmol) in 100 mL of water - MeOH - THF (1:1:4) is treated with lithium hydroxide monohydrate (1.6 g, 38 mmol) and stirred overnight. The reaction mixture is acidified to pH 2 using 1 M aqueous sodium hydrogen sulfate and extracted with two 100 - mL portions of EtOAc. The combined organic layers are washed with two
25 25 - mL portions of saturated aqueous sodium chloride, dried over sodium sulfate and filtered, and the solvents are removed under reduced pressure. Purification by flash chromatography on silica gel eluting with 10% EtOAc - hexanes affords 6.0 g (100%) of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxyhexanoic acid as a gum.
¹H NMR (300 MHz, CDCl₃) δ 3.65 (m, 1H), 2.57 (m, 1H), 1.80-1.30 (m, 7H), 0.95
30 (m, 9H) ppm.

Example 2d; (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxyhexanoic Acid 2-Tetrahydropyranyloxyamide

35 To a stirred solution of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxyhexanoic acid (6.0 g, 32.3 mmol) in 33 mL of dichloromethane at 0 °C is added 2-tetrahydropyranyloxyamine (7.70 g, 65.8 mmol) followed by EDC (7.50 g, 39.4

mmol). The reaction mixture is allowed to warm to 25 °C, stirred 12 h, then diluted with 100 mL of EtOAc and washed successively with 50 mL each of water, 1 M aqueous sodium bisulfate solution, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The combined organic layers are dried over sodium sulfate and filtered, and the solvents are removed under reduced pressure. Purification by flash chromatography on silica gel eluting with 10% EtOAc - hexanes affords 9.0 g (97%) of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxyhexanoic acid 2-tetrahydropyranyloxyamide as a gum.

TLC R_f (hexanes - EtOAc, 1:1) 0.60.

^1H NMR (300 MHz, CDCl_3) δ 8.90 (d, 1H), 5.00 (2s, 1H), 4.00 (m, 1H), 3.62 (m, 2H), 3.01 (t, 1H), 2.21 (m, 1H), 1.90-1.30 (m, 13H), 0.92 (m, 9H) ppm.

Example 2e; (3*R*,4*S*) 3-(2-Methyl-1-propyl)-4-propyl-1-(2-tetrahydropyranyloxy)azetidin-2-one

To a stirred solution of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxyhexanoic acid 2-tetrahydropyranyloxyamide (9.0 g, 31.3 mmol) in 50 mL of anhydrous pyridine at 0 °C is added methanesulfonyl chloride (2.9 mL, 37.6 mmol). The reaction mixture is allowed to stand at 5 °C overnight and the pyridine is removed under reduced pressure. The resulting gum is dissolved in EtOAc (200 mL) and washed successively with 50 mL each of ice-cold 0.1 N hydrochloric acid, dilute aqueous sodium carbonate, and saturated aqueous sodium chloride. The combined organic extracts are dried over sodium sulfate and filtered, and the solvents are removed under reduced pressure affording the methanesulfonate as an off-white solid (11.6 g, 98%) which is used without further purification.

TLC R_f (hexanes - EtOAc, 1:1) 0.75.

^1H NMR (300 MHz, CDCl_3) δ 5.00 (m, 1H), 4.81 (m, 1H), 4.00 (m, 1H), 3.60 (bt, 1H), 3.05 (s, 3H), 2.76-2.60 (m, 1H), 1.92-1.11 (m, 13H), 0.91 (m, 9H) ppm.

A mixture of powdered potassium carbonate (15.0 g, 109 mmol) in 200 mL of acetone is refluxed for 0.5 h then treated with a solution of the above methanesulfonate in 100 mL of acetone and refluxed for an additional 48 h. The resulting slurry is filtered to remove salts and the filtrate is concentrated under reduced pressure. The crude oil is dissolved in 200 mL of EtOAc and washed successively with 50 mL of water and 50 mL of saturated aqueous sodium chloride and the combined organic extracts are dried over sodium sulfate. Filtration and removal of the solvents under pressure affords 8.2 g (96%) of (3*R*,4*S*)-3-(2-methyl-1-

propyl)-4-propyl-1-(2-tetrahydropyranyloxy)azetidin-2-one as a 1:1 mixture of diastereomers which is used without further purification.

TLC R_f (hexanes - EtOAc, 9:1) 0.30.

^1H NMR (300 MHz, CDCl_3) δ 5.20 and 5.04 (two m, 1H), 4.27 and 4.50 (two dt, 1H),
5 4.01-3.89 (m, 1H), 3.68 (m, 1H), 3.05 (m, 1H), 1.92-1.30 (m, 13H), 1.00 (m, 9H)
ppm.

Example 2f; (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoic Acid

10

A solution of the lactam (3*R*,4*S*)-3-(2-methyl-1-propyl)-4-propyl-1-(2-tetrahydropyranyloxy)azetidin-2-one (8.2 g, 30.5 mmol) in 90 mL of dioxane is treated with 53 mL of aqueous 3 N aqueous sodium hydroxide and stirred at 25 °C for 24 h. The reaction mixture is adjusted to pH 2 with 1 M aqueous sodium bisulfate and
15 then extracted with two 100 - mL portions of EtOAc. The combined organic extracts are dried over sodium sulfate and filtered, and the solvents are removed under reduced pressure affording 7.9 g (90%) of crude (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoic acid as a viscous oil which is used without further purification.

20 ^1H NMR (300 MHz, CDCl_3) δ 8.80 (bs, 1H), 4.85 and 4.75 (two m, 1H), 3.95 (m, 1H), 3.60 (m, 1H), 3.19 and 2.87 (two m, 1H), 3.05 (m, 1H), 1.95-1.12 (m, 13H), 0.91 (m, 9H) ppm.

Example 2g; Pentafluorophenyl (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoate

25

A solution of (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoic acid (7.90 g, 27.5 mmol) in 100 mL of anhydrous pyridine is cooled to 0 °C and treated with formic acetic anhydride (4.0 mL, 46 mmol). The reaction
30 mixture is allowed to warm to 25 °C, stirred for 6 h, and then concentrated to dryness under reduced pressure. The resulting gum is dissolved in 150 mL of EtOAc and washed successively with two 50 - mL portions of 1 M aqueous sodium bisulfate and two 50 - mL portions of saturated aqueous sodium chloride. The combined organic extracts are dried over sodium sulfate and filtered, and the solvents are removed under
35 reduced pressure affording 8.67 g (99%) of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoic acid obtained as a viscous oil, which is used without further purification.

¹H NMR (300 MHz, CDCl₃) δ 8.68 and 8.56 (d and s, 1H), 5.07 and 4.81 (two s, 1H), 4.40 (m, 1H), 4.00 (m, 1H), 3.62 (m, 1H), 2.90 and 2.72 (two t, 1H), 2.00-1.20 (m, 13H), 0.98 (m, 9H) ppm.

To a stirred solution of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoic acid (8.67 g, 27.4 mmol) in 50 mL of anhydrous DMF at 0 °C is added pyridine (2.8 mL) and pentafluorophenyl trifluoroacetate (5.9 mL, 33.7 mmol). The reaction mixture is allowed to warm to 25 °C, stirred for 3 h, then poured into water (100 mL) and extracted with EtOAc (250 mL). The organic extracts are then washed with two 50 - mL portions of 1 M aqueous sodium bisulfate, two 50 - mL portions of 1 M aqueous sodium carbonate and are dried over sodium sulfate. Filtration and removal of the solvents under reduced pressure and purification by flash chromatography on silica gel (elution with 10% EtOAc - hexanes) affords 10.1 g (78%) of pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoate as a viscous oil.

¹H NMR (300 MHz, CDCl₃) δ 8.60 and 8.05 (d and s, 1H), 5.07 and 4.83 (m and s, 1H), 4.48 (m, 1H), 4.05 (m, 1H), 3.70 (m, 1H), 3.21 and 3.10 (two dt, 1H), 2.03-1.30 (m, 13H), 1.00 (m, 9H) ppm.

Example 2h; (2*S*)-2-tert-Butoxycarbonylamino-6-benzyloxycarbonylaminohexanoic Acid 1,3-Pyrimidin-2-ylamide

To a solution of (2*S*)-2-amino-6-benzyloxycarbonylaminohexanoic acid (2.00 g, 5.26 mmol) in 5 mL of DMF is added sequentially, HOBt (1.07 g, 7.89 mmol), EDC (1.50 g, 7.89 mmol), 4-methylmorpholine (1.50 g, 10.5 mmol) and 2-aminopyrimidine (0.80 g, 7.89 mmol). The reaction mixture is heated to 50 °C for 2 d, poured into water (50 mL) and extracted with EtOAc (100 mL). The combined organic layers are washed with two 25 - mL portions of saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 50% EtOAc - hexanes affords 2.00 g (83%) of (2*S*)-2-tert-butoxycarbonylamino-6-benzyloxycarbonylaminohexanoic acid 1,3-pyrimidin-2-ylamide as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 8.90 (s, 1H), 8.65 (d, 1H), 8.05 (d, 1H), 7.24 (t, 1H), 7.32 (m, 5H), 7.18 (d, 1H), 4.99 (s, 2H), 4.20 (m, 1H), 3.01 (m, 2H), 1.61 (m, 2H), 1.41-1.23 (m, 4H), 1.40 (s, 9H) ppm.

APCI-MS *m/z* 458 (M+H)⁺.

Example 2; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1*S*)-5-Benzylloxycarbonylamino-1-(1,3-pyrimidin-2-ylcarbamoyl)-1-pentyl]amide

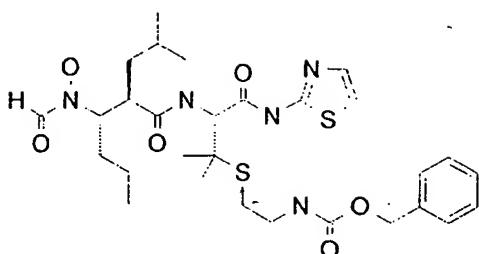
To a solution of (2*S*)-2-tert-butoxycarbonylamino-6-benzyloxycarbonylamino-1,3-pyrimidin-2-ylamide (0.260 g, 0.460 mmol) in 8 mL of dioxane and 4 mL of ethanol is added 4 mL of 4 M hydrogen chloride in dioxane. The reaction mixture is stirred overnight and concentrated *in vacuo* to afford a white solid. DMF (4 mL) is added followed by triethylamine (0.30 mL), a catalytic amount of 1-hydroxybenzotriazole and pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoate (0.221 g, 0.460 mmol). The reaction mixture is warmed at 40 °C for 12 h, poured into water (20 mL) and extracted with two 25 - mL portions of EtOAc. The organic extracts are washed with two 10 - mL portions of 0.1 N hydrochloric acid, two 10 - mL portions of 1 M aqueous sodium carbonate, and one 10 - mL portion of saturated aqueous sodium chloride. The organic solution is dried over sodium sulfate and concentrated under reduced pressure followed by purification by flash chromatography on silica gel affording 0.150 g of the crude product which is dissolved in 10 mL of acetic acid and allowed to stand overnight. Concentration under reduced pressure affords 0.100 g (38%) of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3-pyrimidin-2-ylcarbamoyl)-1-pentyl]amide as a white solid.

¹H NMR (300 MHz, d₆-DMSO) δ 10.90 (s, 1H), 9.75 and 9.44 (two s, 1H), 8.90 (s, 1H), 8.61 (d, 1H), 8.40 (d, 1H), 8.05 (d, 1H), 8.00 (m, 2H), 7.39 (m, 6H), 5.01 (s, 2H), 4.50 and 4.20 (two m, 1H), 3.41 (m, 2H), 3.00 (m, 2H), 2.62 (m, 1H), 1.80-0.61 (m, 13H), 0.81 (m, 9H) ppm.

APCI-MS *m/z* 571 (M+H)⁺.

Anal. Calcd. for C₂₉H₄₂N₆O₆: C, 61.03; H, 7.42; N, 14.73. Found: C, 61.08; H, 7.42; N, 14.64.

Example 3; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1*R*)-2-Methyl-2-(2-benzyloxycarbonylamino-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide



Example 3a; (2*R*)-3-Mercapto-3-methyl-2-tert-butoxycarbonylamino-4-oxobutanoic Acid

To a stirred solution of (2*R*)-2-amino-3-mercapto-3-methylbutanoic acid (25.0 g, 168 mmol) in 150 mL of tert-butanol and 150 mL of 1 M aqueous sodium hydroxide at 0 °C is added di-*tert*-butyl dicarbonate (36.6 g, 108 mmol). After 10 minutes an additional 190 mL of 1 M aqueous sodium hydroxide is added and the reaction mixture is allowed to warm to 25 °C and stirred overnight. The reaction mixture is acidified to pH 2 with solid sodium bisulfate and extracted with EtOAc (200 mL). The organic extracts are dried over sodium sulfate, filtered, and the solvents removed under reduced pressure. The resulting crude solid is recrystallized from hexanes - EtOAc to afford 36 g (88%) of (2*R*)-3-mercapto-3-methyl-2-tert-butoxycarbonylamino-4-oxobutanoic acid as a white solid.

¹H NMR (300 MHz, d₆-DMSO) δ 7.50 (bs, 1H), 5.51 (d, 1H), 4.35 (d, 1H), 2.05 (bs, 1H), 1.59 (s, 3H), 1.48 (s, 9H), 1.46 (s, 3H) ppm.
APCI-MS m/z 248 (M-H)⁺.

Example 3b; (2*R*)-3-(2-Benzoyloxycarbonylamino-1-ethylsulfanyl)-3-methyl-2-tert-butoxycarbonylamino-4-oxobutanoic Acid

To an ice-cold solution of (2*R*)-3-mercapto-3-methyl-2-tert-butoxycarbonylamino-4-oxobutanoic acid (3.00 g, 12.0 mmol) in 12 mL of 1 M aqueous sodium hydroxide is added an ice-cooled solution of 2-bromoethylamine hydrobromide (2.50 g, 12.0 mmol) in 12 mL of 1 M aqueous sodium hydroxide. The reaction mixture is allowed to warm to 25 °C and stirred 24 h. The solution is cooled to 0 °C and treated sequentially with 24 mL of 1 M aqueous sodium hydroxide and benzyl chloroformate (2.00 g, 12 mmol) and stirred for 2 h. The reaction mixture is acidified to pH 2 with 1 M sodium bisulfate and extracted with two 100 - mL portions of EtOAc. The combined organic extracts are washed with two 40 - mL portions of saturated aqueous sodium chloride and dried over sodium sulfate. Concentration under reduced pressure affords 2.80 g (80%) of (2*R*)-3-(2-benzoyloxycarbonylamino-1-ethylsulfanyl)-3-methyl-2-tert-butoxycarbonylamino-4-oxobutanoic acid as a gum.

¹H NMR (300 MHz, CDCl₃) δ 7.39 (m, 5H), 5.50 (m, 1H), 5.17 (s, 2H), 4.30 (m, 1H), 3.40 (m, 2H), 2.75 (m, 2H), 1.50 (s, 12H), 1.40 (s, 3H) ppm.

Example 3c; (2*R*)-3-(2-Benzoyloxycarbonylamino-1-ethylsulfanyl)-3-methyl-2-tert-butoxycarbonylaminobutanoic Acid 1,3-Thiazol-2-ylamide

To a solution of (2*R*)-3-(2-benzoyloxycarbonylamino-1-ethylsulfanyl)-3-methyl-2-tert-butoxycarbonylaminobutanoic acid (2.80 g, 6.60 mmol) in 10 mL of acetonitrile at 0 °C is added 1,1'-carbonyldiimidazole (1.20 g, 6.6 mmol). After 10 min 2-amino-1,3-thiazole (0.65 g, 6.6 mmol) is added. The reaction mixture is heated at 50 °C and stirred for 12 h then poured into water (50 mL) and extracted with two 50 - mL portions of EtOAc. The combined organic extracts are washed with two 25 - mL portions of saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated under reduced pressure. Purification by chromatography on silica gel (elution with 20% EtOAc - hexanes followed by 50% EtOAc - hexanes) affords 0.65 g (19%) of (2*R*)-3-(2-benzoyloxycarbonylamino-1-ethylsulfanyl)-3-methyl-2-tert-butoxycarbonylaminobutanoic acid 1,3-thiazol-2-ylamide as a foam.

¹H NMR (300 MHz, CDCl₃) δ 12.30 (s, 1H), 7.45 (d, 1H), 7.30 (m, 5H), 7.20 (d, 1H), 7.01 (m, 1H), 4.97 (s, 2H), 4.45 (d, 1H), 3.09 (m, 2H), 2.62 (m, 2H), 1.38 (s, 9H), 1.23 (s, 3H), 1.19 (s, 3H) ppm.

Example 3; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1*R*)-2-Methyl-2-(2-benzoyloxycarbonylamino-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbonyl)-1-propyl]amide

To a solution of (2*R*)-3-(2-benzoyloxycarbonylamino-1-ethylsulfanyl)-3-methyl-2-tert-butoxycarbonylaminobutanoic acid 1,3-thiazol-2-ylamide (0.300 g, 0.600 mmol) in 4 mL of dioxane and 4 mL of ethanol is added 4 mL of 4 M hydrogen chloride in dioxane. The reaction mixture is stirred overnight and concentrated to a white solid. DMF (4 mL) is added followed by triethylamine (0.30 mL, 2.0 mmol), a catalytic amount of HOBt, and pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoate (0.290 g, 0.290 mmol). The reaction mixture is warmed at 50 °C for 12 h, poured into water (10 mL) and extracted with two 15 - mL portions of EtOAc. The organic extracts are washed with two 10 - mL portions of 0.1 N hydrochloric acid, two 10 - mL portions of 1 M aqueous sodium carbonate, and saturated aqueous sodium chloride. Drying over sodium sulfate and removal of the solvents under reduced pressure followed by

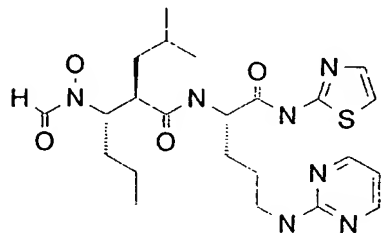
purification by silica gel chromatography affords 0.100 g of the crude product which is dissolved in 10 mL of acetic acid and allowed to stand overnight. Concentration under reduced pressure affords 0.062 g (17%) of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic acid [(1*R*)-2-methyl-2-(2-benzyloxycarbonylamino-1-ethylsulfanyl)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as a white solid.

¹H NMR (300 MHz, d₆-DMSO) δ 12.40 (bs, 1H), 9.75 and 9.45 (two bs, 1H), 8.41 (m, 1H), 8.40 and 7.98 (two s, 1H), 7.45 (d, 1H), 7.20 (m, 6H), 7.06 (m, 1H), 5.01 and 4.51 (two m, 3H), 4.20 (m, 0.4), 3.41 (m, 1H), 3.20 (m, 2H), 2.81 (m, 1H), 2.70 (2H), 1.70-0.42 (m, 22H) ppm.

ESI-MS *m/z* 620 (M-H)⁺.

Anal. Calcd. for C₂₉H₄₃N₅O₆S₂: C, 56.02; H, 6.97; N, 11.26; S, 10.31. Found: C, 55.86; H, 7.06; N, 11.11; S, 10.18.

Example 4; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1*S*)-4-(1,3-Pyrimidin-2-ylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide



Example 4a; (2*S*)-2-tert-Butoxycarbonylamino-5-aminopentanoic Acid

A mixture of (2*S*)-2-tert-butoxycarbonylamino-5-benzyloxycarbonylamino-5-aminopentanoic acid (25 g, 68.3 mmol) and 3 g of 5% palladium on carbon (50 wt. % water content) in 200 mL of ethanol is stirred overnight under hydrogen gas at 1 atmosphere pressure. Filtration and concentration of the filtrate under reduced pressure affords 15 g (95%) of (2*S*)-2-tert-butoxycarbonylamino-5-aminopentanoic acid as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 7.80 (m, 1H), 3.30 (bs, 3H), 2.69 (m, 1H), 1.70-1.22 (m, 4H), 1.31 (s, 9H) ppm.

Example 4b; (2*S*)-2-tert-Butoxycarbonylamino-5-(1,3-pyrimidin-2-yl)aminopentanoic Acid

A mixture of (2*S*)-2-tert-butoxycarbonylamino-5-aminopentanoic acid (0.50 g, 2.16 mmol), potassium carbonate (0.60 g, 4.31 mmol) and 2-chloropyrimidine (0.25 g, 2.16 mmol) in 5 mL of DMF is stirred and heated at 80 °C

for 3 d. The reaction mixture is then poured into a dilute solution of acetic acid (50 mL) and extracted with three 25 - mL portions of dichloromethane. The combined organic extracts are washed with two 25 - mL portions of saturated aqueous sodium chloride and dried over sodium sulfate. Concentration under reduced pressure affords
5 0.40 g (67%) of (2*S*)-2-tert-butoxycarbonylamino-5-(1,3-pyrimidin-2-yl)aminopentanoic acid as a gum which is used without further purification.
¹H NMR (300 MHz, d₆-DMSO) δ 12.40 (bs, 1H), 8.22 (d, 2H), 7.10 (m, 2H), 6.52 (t, 1H), 3.90 (m, 1H), 3.22 (m, 2H), 1.75-1.32 (m, 4H), 1.39 (s, 9H) ppm.

10

Example 4c; (2*S*)-2-tert-Butoxycarbonylamino-5-(1,3-pyrimidin-2-yl)aminopentanoic Acid 1,3-Thiazol-2-ylamide

To a solution of (2*S*)-2-tert-butoxycarbonylamino-5-(1,3-pyrimidin-2-yl)aminopentanoic acid (0.40 g, 1.3 mmol) in 2 mL of dichloromethane at 0 °C is
15 added 1,1'-carbonyldiimidazole (0.23 g, 1.2 mmol). After 10 minutes 2-amino-1,3-thiazole (0.13 g, 1.0 mmol) is added. The reaction mixture is stirred for 12 h then poured into water (50 mL) and extracted with two 50 - mL portions of EtOAc. The combined organic extracts are washed with two 25 - mL portions of saturated aqueous
20 sodium chloride and dried over sodium sulfate. The mixture is concentrated under reduced pressure and the crude product purified by flash chromatography on silica gel (elution with 50% EtOAc - hexanes followed by EtOAc) affording 0.274 g (55%) of the title compound (2*S*)-2-tert-butoxycarbonylamino-5-(1,3-pyrimidin-2-yl)aminopentanoic acid 1,3-thiazol-2-ylamide as a yellow foam.
25 ¹H NMR (300 MHz, CDCl₃) δ 8.28 (d, 2H), 7.52 (d, 1H), 7.30 (s, 1H), 7.00 (d, 1H), 6.51 (t, 1H), 6.20 (m, 1H), 5.70 (d, 1H), 4.60 (m, 1H), 3.60-3.38 (m, 2H), 2.15-1.61 (m, 4H), 1.49 (s, 9H) ppm.

Example 4; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid
30 [(1*S*)-4-(1,3-Pyrimidin-2-ylamino)-1-(1,3-thiazol-2-ylcarbonyl)-1-butyl]amide

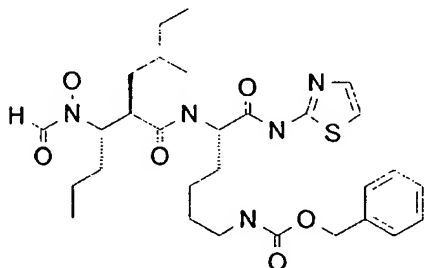
To a solution of (2*S*)-2-tert-butoxycarbonylamino-5-(1,3-pyrimidin-2-yl)aminopentanoic acid 1,3-thiazol-2-ylamide (0.274 g, 0.68 mmol) in 4 mL of dioxane and 4 mL of ethanol is added 4 mL of 4 M hydrogen chloride in dioxane.
35 The reaction mixture is stirred overnight and concentrated to a white solid. DMF (4 mL) is added followed by triethylamine (0.30 mL, 2.0 mmol), a catalytic amount of HOBt, and pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-

methyl-1-propyl)hexanoate (0.33 g, 0.69 mmol). The reaction mixture is warmed at 50 °C for 12 h, poured into water (10 mL) and extracted with two 20 - mL portions of EtOAc. The organic extracts are washed with two 25 - mL portions of 0.1 N hydrochloric acid, two 25 - mL portions of 1 M aqueous sodium carbonate, and saturated aqueous sodium chloride. Drying over sodium sulfate and concentration under reduced pressure is followed by purification by silica gel chromatography (elution with 50% EtOAc - hexanes followed by EtOAc) affording 0.100 g of the crude product which is dissolved in 10 mL of acetic acid and allowed to stand overnight. Concentration under reduced pressure affords 0.082 g (20%) of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic acid [(1*S*)-4-(1,3-pyrimidin-2-ylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide as a white solid.

¹H NMR (300 MHz, d₆-DMSO) δ 12.20 (bs, 1H), 9.72 and 9.42 (two bs, 1H), 8.50 (m, 1H), 8.38 and 7.99 (s and d, 1H), 8.22 (d, 2H), 7.49 (d, 1H), 7.20 (m, 2H), 6.55 (t, 1H), 4.58 (m, 1H), 4.20 and 3.42 (t and m, 1H), 3.30 (m, 2H), 2.65 (m, 1H), 1.81-0.90 (m, 11H), 0.82 (d, 3H), 0.71 (m, 6H) ppm.

Anal. Calcd. for C₂₃H₃₅N₇O₄S: C, 54.63; H, 6.98; N, 19.39; S, 6.34. Found: C, 54.47; H, 7.09; N, 19.23; S, 6.21.

Example 5; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-butyl)hexanoic Acid
[(1*S*)-5-Benzoyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide



Example 5a; Ethyl (2*R*,3*R*)-2-(2-Methyl-1-butyl)-3-hydroxyhexanoate

Diisopropylamine (3.92 mL, 30.0 mmol) is dissolved in 30 mL of anhydrous THF and cooled using an ice water bath. n-Butyllithium (16.5 mL, 2.0 M solution in cyclohexane, 27.5 mmol) is added dropwise over 10 min and the resulting pale yellow solution cooled to -78 °C. A 15 - mL THF solution of ethyl (3*R*)-3-hydroxyhexanoate (2.00 g, 12.5 mmol) is added over 10 min and the mixture is stirred at -78 °C for 30 min. 2-Methyl-1-butyl iodide (3.70 g, 18.7 mmol) is dissolved in 10 mL of a 1:1 THF - HMPA solution and added to the reaction mixture. The resulting solution is allowed to warm slowly to 0 °C over 3 h. After stirring overnight at 4 °C 250 mL of a 5% aqueous citric acid solution is added and the organics are extracted

with two 250 - mL portions of ether and then washed with saturated aqueous sodium chloride. The organics are then dried over sodium sulfate and concentrated *in vacuo*. Chromatography on silica gel (elution with 25% EtOAc - hexanes) gives ethyl (2*R*,3*R*)-2-(2-methyl-1-butyl)-3-hydroxyhexanoate as a pale yellow oil (0.85 g, 30% yield).

¹H NMR (400 MHz, CDCl₃) δ 4.18 (q, 2H), 3.64 (m, 1H), 2.56 (m, 1H), 2.40 (d, 1H), 1.96-0.94 (m, 21H) ppm.

Example 5b; (2*R*,3*R*)-2-(2-Methyl-1-butyl)-3-hydroxyhexanoic Acid

Ethyl (2*R*,3*R*)-2-(2-methyl-1-butyl)-3-hydroxyhexanoate (0.85 g, 3.65 mmol) is dissolved in 3:1:1 THF - MeOH - water (10 mL). To this is added lithium hydroxide monohydrate (0.46 g, 10.9 mmol). The reaction is stirred for 18 h at 25 °C and then is extracted with ether. The aqueous layer is acidified with solid sodium bisulfate and then extracted with two 100 - mL portions of ether. The combined organics are washed with saturated aqueous sodium chloride and dried over sodium sulfate. Concentration under reduced pressure affords (2*R*,3*R*)-2-(2-methyl-1-butyl)-3-hydroxyhexanoic acid as an off-white solid (0.66 g, 89% yield).

¹H NMR (300 MHz, CDCl₃) δ 3.68 (m, 1H), 2.56 (m, 1H), 1.85-0.94 (m, 18H) ppm.

Example 5c; (2*R*,3*R*)-2-(2-Methyl-1-butyl)-3-hydroxyhexanoic Acid 2-Tetrahydropyranyloxyamide

(2*R*,3*R*)-2-(2-Methyl-1-butyl)-3-hydroxyhexanoic acid (0.66 g, 3.25 mmol) is dissolved in 6 mL of anhydrous dichloromethane. EDC (0.69 g, 3.57 mmol) is added followed by 2-tetrahydropyranyloxyamine (0.76 g, 6.50 mmol). The reaction stirred at 25 °C for 8 h and is then poured into 50 mL of 1 M hydrochloric acid. The mixture is extracted with two 100 - mL portions of dichloromethane. The combined organics are then washed with saturated aqueous sodium chloride and dried over sodium sulfate. Concentration under reduced pressure affords (2*R*,3*R*)-2-(2-methyl-1-butyl)-3-hydroxyhexanoic acid 2-tetrahydropyranyloxyamide as a foam (0.65 g, 66% yield).

¹H NMR (300 MHz, CDCl₃) δ 8.45 (two s, 1H), 4.96 (two s, 1H), 3.95 (m, 1H), 3.64 (m, 2H), 2.75 (two d, 1H), 2.20 (m, 1H), 1.83-0.92 (m, 24H) ppm.

Example 5d; (3*R*,4*S*) 3-(2-Methyl-1-butyl)-4-propyl-1-(2-tetrahydropyranyloxy)azetidin-2-one

(2*R*,3*R*)-2-(2-Methyl-1-butyl)-3-hydroxyhexanoic acid 2-tetrahydropyranyloxyamide (0.65 g, 2.14 mmol) is dissolved in 5 mL of pyridine and cooled to 0 °C. Methanesulfonyl chloride (0.19 mL, 2.46 mmol) is added dropwise and the reaction stirred for 6 h at 0 °C. The reaction is poured into 10 mL of ice cold 2 M hydrochloric acid and the mixture extracted with two 25 - mL portions of EtOAc. The combined organics are washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated to afford the crude methanesulfonate which is used with no further purification (0.80 g 99% yield).

¹H NMR (300 MHz, CDCl₃) δ 8.38 and 8.31 (two s, 1H), 4.95 (m, 1H), 4.74 (m, 1H), 3.93 (m, 1H), 3.62 (m, 1H), 3.01 (s, 3H), 2.50 (m, 1H), 1.85-0.95 (m, 24H) ppm.

Potassium carbonate (0.87 g, 6.32 mmol) is added to 10 mL of acetone and the suspension is refluxed for 1 h. The above methanesulfonate (0.80 g, 2.11 mmol) is dissolved in 5 mL of acetone and then added to the refluxing mixture. The resulting thick slurry is refluxed for 16 h and is cooled to 25 °C and filtered. The filter cake is washed several times with EtOAc and the filtrate is concentrated under reduced pressure to provide (3*R*,4*S*)-3-(2-methyl-1-butyl)-4-propyl-1-(2-tetrahydropyranyloxy)azetidin-2-one as an oil (0.42 g, 70% yield).

¹H NMR (300 MHz, CDCl₃) δ 5.18 and 5.01 (two s, 1H), 4.23 and 4.14 (two m, 1H), 3.90 (m, 1H), 3.63 (m, 1H), 3.02 (m, 1H), 1.85-0.85 (m, 24H) ppm.

Example 5e; (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoic Acid

(3*R*,4*S*)-3-(2-Methyl-1-butyl)-4-propyl-1-(2-tetrahydropyranyloxy)azetidin-2-one (0.42 g, 1.48 mmol) is dissolved in 2.5 mL of 1,4-dioxane. 2.5 N Aqueous sodium hydroxide (1.78 mL, 4.45 mmol) is added and the reaction is stirred for 18 h at 25 °C. The solution is diluted with 50 mL of ether. The organic layer is separated and discarded. The aqueous layer is acidified with solid sodium bisulfate and then extracted with two 25 - mL portions of ether. The organics are dried over sodium sulfate and concentrated *in vacuo* to provide (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoic acid as an oil which is used without further purification (0.44 g, 98% yield).

¹H NMR (300 MHz, CDCl₃) δ 4.84 and 4.74 (two m, 1H), 4.03 and 3.94 (two m, 1H), 3.61 (m, 1H), 3.14-3.02 and 2.92 (two m, 2H), 1.84-0.86 (m, 24H) ppm.

APCI-MS *m/z* 300 (M-H).

Example 5f; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoic Acid

(2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoic acid
5 (0.44 g, 1.46 mmol) is dissolved in 5 mL of pyridine. Formic acetic anhydride (0.26 mL, 2.92 mmol) is added at 25 °C. The reaction is stirred for an additional 6 h at 25 °C and then poured into 25 mL of ice cold 1 M hydrochloric acid. The organics are extracted with two 50 - mL portions of dichloromethane. The combined organic phases are washed with saturated aqueous sodium chloride, dried over sodium sulfate,
10 and concentrated under reduced pressure to give (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoic acid as a clear oil used without further purification (0.40 g, 83% yield).
APCI-MS *m/z* 328 (M-H).

15 Example 5g; Pentafluorophenyl (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoate

(2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoic acid (0.40 g, 1.21 mmol) is dissolved in 3 mL of dichloromethane and
20 pyridine (0.11 mL, 1.34 mmol) is added. Pentafluorophenyl trifluoroacetate (0.23 mL, 1.34 mmol) is added and the reaction continued to stir at 25 °C for 18 h. The reaction mixture is poured into 25 mL of 1 M hydrochloric acid and the organics extracted with two 50 - mL portions of dichloromethane. The combined organic phases are washed with 10% aqueous sodium carbonate, dried over sodium sulfate, and
25 concentrated *in vacuo* to give an amber oil. Chromatography of the crude product on silica gel (elution with 10% EtOAc - hexanes) gave pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoate as a clear viscous oil (0.41 g, 68% yield).

¹H NMR (300 MHz, CDCl₃) δ 8.56 and 8.02 (two d, 1H), 5.04 and 4.83 (two m, 1H),
30 4.57 (m, 1H), 3.99 (m, 1H), 3.64 (m, 1H), 3.24 and 3.10 (two dt, 1H), 2.03-0.86 (m, 24H) ppm.

Example 5h; (2*S*)-6-Benzylloxycarbonylamino-2-tert-butoxycarbonylaminohexanoic Acid 1,3-Thiazol-2-ylamide

35

To a solution of (2*S*)-6-benzylloxycarbonylamino-2-tert-butoxycarbonylaminohexanoic acid (15.0 g, 37.1 mmol) in 100 mL of DMF at 0 °C is

added, sequentially, HOBt (6.0 g, 44.4 mmol), N-methylmorpholine (12.0 mL, 109 mmol), and EDC (8.5 g, 44.3 mmol). After 30 min at 0 °C 2-amino-1,3-thiazole (3.7 g, 37 mmol) is added. The reaction mixture is stirred at 0 °C for 30 min and is heated at 50 °C for 1 h. The mixture is allowed to cool to 25 °C and is concentrated *in vacuo*.

- 5 The residue is diluted with 250 mL of EtOAc. The organic phase is washed with water, saturated aqueous sodium chloride, and is dried over magnesium sulfate and concentrated under reduced pressure. The crude product is chromatographed on silica gel (elution with 30% EtOAc - hexanes followed by 70% EtOAc - hexanes) to provide 16.5 g (92%) of (2*S*)-6-benzyloxycarbonylamino-2-tert-
- 10 butoxycarbonylamino-hexanoic acid 1,3-thiazol-2-ylamide as a foam;
¹H NMR (300 MHz, CDCl₃) δ 7.60 (d, 1H), 7.39 (bs, 5H), 7.03 (d, 1H), 5.50 (bd, 1H), 5.08 (bs, 1H), 5.11 (s, 2H), 4.90 (bs, 1H), 4.51 (bs, 1H), 3.20 (dd, 2H), 1.92 (m, 1H), 1.79 (m, 1H), 1.52 (m, 4H), 1.47 (s, 9H) ppm.

- 15 Example 5i; (2*S*)-6-Benzyloxycarbonylamino-2-aminohexanoic Acid 1,3-Thiazol-2-ylamide

- A solution of (2*S*)-6-benzyloxycarbonylamino-2-tert-
- 20 butoxycarbonylamino-hexanoic acid 1,3-thiazol-2-ylamide (16.5 g, 34.0 mmol) in 150 mL of dichloromethane is treated dropwise at 25 °C with 60 mL of trifluoroacetic acid. The mixture is stirred for 4 hr at 25 °C. The mixture is concentrated *in vacuo*. The residue is diluted with 50 mL of dichloromethane and stirred at 0 °C. The mixture is made basic (pH 8) with saturated aqueous potassium carbonate. The mixture is then extracted with three 70 - mL portions of dichloromethane. The organic phases
- 25 are combined, dried over magnesium sulfate, and concentrated *in vacuo* to provide 10.8 g (86%) of (2*S*)-6-benzyloxycarbonylamino-2-aminohexanoic acid 1,3-thiazol-2-ylamide as a solid.
¹H NMR (300 MHz, CDCl₃) δ 7.50 (d, 1H), 7.40 (bs, 5H), 7.38 (d, 1H), 5.13 (bs, 2H), 4.83 (bs, 1H), 3.60 (dd, 1H), 3.26 (dd, 2H), 2.00 (m, 1H), 2.60 (m, 5H) ppm.

- 30 Example 5j; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoic Acid [(1*S*)-5-Benzyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbonyl)-1-pentyl]amide

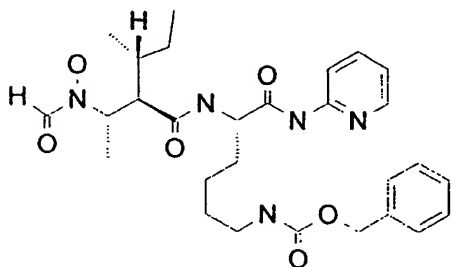
- 35 Pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoate (0.10 g, 0.20 mmol) is dissolved in 2.5 mL of anhydrous DMF. To this solution is added HOBt (.003 g, 0.02 mmol) followed by (2*S*)-6-

- benzyloxycarbonylamino-2-aminohexanoic acid 1,3-thiazol-2-ylamide (0.09 g, 0.24 mmol). The reaction is heated at 50 °C for 16 h. The mixture is diluted with 1:1 hexanes - EtOAc solution and the organic phase is washed with 10% aqueous sodium carbonate, 1 M hydrochloric acid, and saturated aqueous sodium chloride. The organics are dried over sodium sulfate, concentrated *in vacuo*, and then chromatographed on silica gel (elution with 50% EtOAc - hexanes) to give (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide (0.06 g, 46% yield).
- APCI-MS m/z 696 ($M+Na$)⁺.

Example 5; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-butyl)hexanoic Acid [(1*S*)-5-Benzyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide

- (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-butyl)hexanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide (0.06 g, 0.09 mmol) is dissolved in 2 mL of 80% aqueous acetic acid and stirred overnight at 45 °C. After cooling to 25 °C 2 mL of water is added and the product is filtered to give (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-butyl)hexanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide as a white solid (0.03 g, 74% yield).
- ¹H NMR (300 MHz, CD₃OD) δ 8.36 and 7.95 (two s, 1H), 7.42 (d, 1H), 7.32 (m, 5H), 7.10 (d, 1H), 5.05 (s, 2H), 4.61 (m, 1H), 4.35 and 3.58 (two dt, 1H), 3.12 (t, 2H), 2.89-2.79 (m, 1H), 1.93-0.76 (m, 24H) ppm.
- ESI-MS m/z 612 ($M+Na$)⁺, 588 ($M-H$)⁻.
- Anal. Calcd for C₂₉H₄₃N₅SO₆: C, 59.06; H, 7.35; N, 11.88; Found: C, 59.48; H, 7.43; N, 11.79.

- Example 6; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-[(2*R*)-2-butyl]butanoic Acid [(1*S*)-5-Benzyloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide



Example 6a; (2*E*)-2-Buten-1-yl (3*R*)-3-Hydroxybutyrate

A mixture of ethyl (3*R*)-3-hydroxybutyrate (15 g, 0.127 mol), (E)-crotyl alcohol (100 g, 1.39 mol) and titanium tetraisopropoxide (3.5 g, 0.012 mol) are heated at 70 °C overnight under a stream of argon. The reaction mixture is cooled to 25 °C and treated with 5 mL of saturated aqueous sodium bicarbonate and stirred vigorously for 1 h to destroy catalyst. The resulting slurry is dried using sodium sulfate, filtered, and the crotyl alcohol is removed under reduced pressure (40 °C, 5 mm Hg, then 20 °C, 0.10 mm Hg) affording 12 g (60%) of (2*E*)-2-buten-1-yl (3*R*)-3-hydroxybutyrate as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 5.81 (dq, 1H), 5.60 (dt, 1H), 4.55 (d, 2H), 4.21 (m, 1H), 3.12 (d, 1H), 2.51 (dd, 1H), 2.42 (dd, 1H), 1.71 (d, 3H), 1.22 (d, 3H) ppm.

Example 6b; (2*R*,3*R*)-2-(3-Buten-2-yl)-3-hydroxybutanoic Acid

To a stirred solution of diisopropylamine (4.4 mL, 31.5 mmol) in 60 mL of anhydrous 1,2-dimethoxyethane at -78 °C is added dropwise 19.7 mL (31.5 mmol) of 1.6 M *n*-butyllithium in hexanes over 10 minutes. After 1 h, (2*E*)-2-buten-1-yl (3*R*)-3-hydroxybutanoate (2.0 g, 12.6 mmol) is added dropwise over several minutes and the cooling bath is removed, the reaction mixture is allowed to warm to 25 °C, then is heated at 60 °C for 12 h. The resulting slurry is cooled to 25 °C, treated with 75 mL of 0.25 M aqueous sodium hydroxide, and extracted with two 50 - mL portions of ether. The aqueous layer is then acidified to pH 2 using concentrated hydrochloric acid (with ice cooling) and then is extracted with five 100 - mL portions of chloroform. The combined organic extracts are dried over sodium sulfate and filtered, and the solvents are removed under reduced pressure affording 1.50 g (75%) of (2*R*,3*R*)-2-(2-butyl)-3-hydroxybutanoic acid as an 80:20 mixture of diastereomers at the 2-butyl stereocenter.

¹H NMR (300 MHz, CDCl₃) major isomer δ 7.00 (bs, 1H), 5.80 (m, 1H), 5.10 (s, 1H), 4.99 (s, 1H), 4.07 (m, 1H), 2.62 (m, 1H), 2.30 (dd, 1H), 1.30 (d, 3H), 1.15 (d, 3H) ppm; minor isomer δ 2.25 (dd), 1.29 (t), 1.09 (t) ppm.

Example 6c; (2*R*,3*R*)-2-(3-Buten-2-yl)-3-hydroxybutanoic Acid 2-Tetrahydropyranyloxyamide

To a stirred solution of (2*R*,3*R*)-2-(3-buten-2-yl)-3-hydroxybutanoic acid (2.30 g, 14.6 mmol) in 15 mL of dichloromethane at 0 °C is added 2-tetrahydropyranyloxyamine (3.40 g, 21.1 mmol) followed by EDC (3.30 g, 17.4

mmol). The reaction mixture is allowed to warm to 25 °C, stirred 12 h, then is diluted with 100 mL of EtOAc and washed successively with water, 1 M aqueous sodium bisulfate, 1 M aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The combined organic layers are dried over sodium sulfate and concentrated under reduced pressure. Purification by chromatography on silica gel eluting with 50% EtOAc - hexanes affords 2.90 g (78%) of (2*R*,3*R*)-2-(3-buten-2-yl)-3-hydroxybutanoic acid 2-tetrahydropyranyloxyamide as an oil.

¹H NMR (300 MHz, CDCl₃) δ 8.85 (two s, 1H), 5.80 (m, 1H), 5.25-4.80 (m, 3H), 4.20-3.91 (m, 2H), 3.61 (m, 1H), 3.50 and 3.35 (two d, 1H), 2.70 (m, 1H), 2.41 and 2.30 (two m, 1H), 1.90-1.50 (m, 6H), 1.29 (d, 3H), 1.15 (d, 3H) ppm; minor isomer δ 9.10, 8.72 (two s), 3.20 (m), 1.10 (d) ppm.

Anal. Calcd for C₁₃H₂₃NO₄: C, 60.68; H, 9.00; N, 5.44. Found: C, 60.40; H, 8.92; N, 5.50.

15 Example 6d; (3*R*,4*S*)-3-[(2*R*)-3-Buten-2-yl]-4-methyl-1-(2-tetrahydropyranyloxy)azetidin-2-one

To a stirred solution of (2*R*,3*R*)-2-[(2*R*)-3-buten-2-yl]-3-hydroxybutanoic acid 2-tetrahydropyranyloxyamide (2.80 g, 10.9 mmol) in 10 mL of anhydrous pyridine at 0 °C is added methanesulfonyl chloride (1.0 mL, 13 mmol). The reaction mixture is allowed to warm to 25 °C, is stirred overnight, and the pyridine is removed under reduced pressure. The resulting gum is dissolved in EtOAc (100 mL) and washed successively with 25 mL each of ice-cold 0.1 N hydrochloric acid, dilute aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The combined organic extracts are dried over sodium sulfate. Concentration under reduced pressure affords the methanesulfonate as a solid which is used without further purification.

A mixture of powdered potassium carbonate (5.0 g, 33 mmol) in 100 mL of acetone is refluxed for 0.5 h then treated with a solution of the above methanesulfonate in 10 mL of acetone and refluxed for an additional 48 h. The resulting slurry is allowed to cool to 25 °C, then is filtered and the filtrate is concentrated under reduced pressure. The crude oil is dissolved in 100 mL of EtOAc and washed successively with water and saturated aqueous sodium chloride. The combined organics are dried over sodium sulfate. Concentration under reduced pressure followed by purification by silica gel chromatography (elution with 20% EtOAc - hexanes) affords 1.40 g (54%) of (3*R*,4*S*)-3-(3-buten-2-yl)-4-methyl-1-(2-tetrahydropyranyloxy)azetidin-2-one.

¹H NMR (300 MHz, CDCl₃) δ 6.10 (m, 1H), 5.15, 5.12, 5.10, 5.01 (four s, 3H), 4.20-4.00 (m, 2H), 3.65 (m, 1H), 2.85 (dd, 1H), 2.55 (m, 1H), 1.90-1.55 (m, 6H), 1.42 (two d, 3H), 1.12 and 1.09 (two d, 3H) ppm.

Anal. Calcd. for C₁₃H₂₁NO₃: C, 65.23; H, 8.84; N, 5.85. Found: C, 65.10; H, 8.85; N, 5.83.

Example 6e; (3*R*,4*S*)-3-[(2*R*)-2-butyl]-4-methyl-1-(2-tetrahydropyranyloxy)azetidin-2-one

A mixture of (3*R*,4*S*)-3-(3-buten-2-yl)-4-methyl-1-(2-tetrahydropyranyloxy)azetidin-2-one (1.40 g, 5.86 mmol) and 0.15 g of 5% palladium on barium sulfate in 10 mL of EtOAc is stirred overnight under hydrogen at 1 atmosphere pressure. The reaction mixture is filtered and the filtrate is concentrated under reduced pressure affording 1.3 g (93%) of (3*R*,4*S*)-3-(2-butyl)-4-methyl-1-(2-tetrahydropyranyloxy)azetidin-2-one.

¹H NMR (300 MHz, CDCl₃) δ 5.20 and 5.01 (two s, 1H), 4.21 and 4.00 (two dd, 1H), 3.61 (m, 1H), 2.75 (dd, 1H), 2.00 (m, 1H), 1.82-1.50 (m, 6H), 1.38 (two d, 3H), 1.28 (m, 1H), 0.94 (t, 3H), 0.91 (d, 3H) ppm.

Example 6f; (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-butyl)butanoic Acid

A solution of (3*R*,4*S*)-3-(2-butyl)-4-methyl-1-(2-tetrahydropyranyloxy)azetidin-2-one (1.30 g, 5.44 mmol) in 15 mL of dioxane is treated with 10 mL of 3 N aqueous sodium hydroxide and stirred at 25 °C for 24 h.

The reaction mixture is adjusted to pH 2 with 1 M aqueous sodium bisulfate and then is extracted with two 25 - mL portions of EtOAc. The combined organic extracts are dried over sodium sulfate and concentrated under reduced pressure affording 1.1 g (85%) of (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-butyl)butanoic acid as an oil.

¹H NMR (300 MHz, CDCl₃) δ 4.90-4.72 (m, 1H), 4.20-3.90 (m, 1H), 3.60 and 3.45 (m, 2H), 2.75 and 2.72 (two dd, 1H), 2.00-1.41 (m, 6H), 1.30 and 1.05 (two d, 3H), 1.82 (m, 8H) ppm.

APCI-MS m/z 258 (M-H)⁺.

Example 6g; Pentafluorophenyl (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-butyl)butanoate

A solution of (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-butyl)butanoic acid (1.10 g, 4.28 mmol) in 10 mL of anhydrous pyridine is cooled to 0 °C and treated with formic acetic anhydride (1.0 mL, 11.5 mmol). The reaction mixture is allowed to warm to 25 °C, stirred for 6 h, and then is concentrated to dryness under reduced pressure. The resulting gum is dissolved in 100 mL of EtOAc and washed successively with two 25 - mL portions of 1 M sodium bisulfate and two 25 - mL portions of saturated aqueous sodium chloride. The combined organic extracts are dried over sodium sulfate and concentrated under reduced pressure affording 1.00 g (97%) of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-butyl)butanoic acid as a viscous oil which is used without further purification.

APCI-MS *m/z* 286 (M-H).

To a stirred solution of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-butyl)butanoic acid (1.00 g, 3.90 mmol) in 8 mL of anhydrous DMF at 0 °C is added pyridine (0.50 mL, 5.9 mmol) and pentafluorophenyl trifluoroacetate (0.92 mL, 5.40 mmol). The reaction mixture is allowed to warm to 25 °C, stirred for 3 h, then is poured into water (50 mL) and extracted with EtOAc (100 mL). The organic extracts are then washed successively with two 25 - mL portions of 1 M sodium bisulfate, two 25 - mL portions of 1 M aqueous sodium carbonate, and are dried over sodium sulfate. Concentration under reduced pressure and purification of the crude product by chromatography on silica gel (elution with 10% EtOAc - hexanes) affords 1.10 g (58%) of pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-butyl)butanoate as a viscous oil.

¹H NMR (300 MHz, CDCl₃) δ 8.70 and 8.10 (three s, 1H), 5.07, 4.81, 4.61 (three m, 1H), 4.00 (m, 1H), 3.61 (m, 1H), 2.00-1.60 (m, 6H), 1.48 and 1.42 (two d, 3H), 1.16 and 1.13 (two d, 3H), 1.16 and 1.13 (two d, 3H), 0.98 (t, 3H), 1.16-1.10 (m, 2H), 1.12 (dd, 1H) ppm.

Anal. Calcd for C₂₀H₂₄NO₅F₅: C, 52.91; H, 5.33; N, 3.10. Found: C, 53.00; H, 5.33; N, 3.08.

Example 6h; (2*S*)-6-Benzylloxycarbonylamino-2-tert-butoxycarbonylaminohexanoic Acid 2-Pyridylamide

To a solution of (2*S*)-6-benzylloxycarbonylamino-2-tert-butoxycarbonylaminohexanoic acid (3.00 g, 7.89 mmol) in 15 mL of DMF is added, sequentially, HOBt (1.07 g, 7.89 mmol), EDC (1.97 g, 10.3 mmol), 4-methylmorpholine (1.60 g, 15.8 mmol) and 2-aminopyridine (0.97 g, 10.25 mmol). The reaction mixture is heated to 50 °C for 2 d, poured into water (100 mL) and

extracted with EtOAc (200 mL). The combined organic layers are washed with two 100 - mL portions of saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated under reduced pressure. Purification by chromatography on silica gel (elution with 20% EtOAc - hexanes followed by 50% EtOAc - hexanes) affords 1.50 g (42%) of the title compound as a white foam.

¹H NMR (300 MHz, CDCl₃) δ 9.60 (bs, 1H), 8.32 (d, 1H), 8.25 (d, 1H), 7.80 (t, 1H), 7.35 (m, 5H), 7.11 (t, 1H), 5.37 (d, 1H), 5.10 (s, 2H), 4.94 (m, 1H), 4.30 (m, 1H), 3.20 (m, 2H), 1.97 (m, 1H), 1.75 (m, 1H), 1.60-1.41 (m, 6H), 1.45 (s, 9H) ppm.

10 Example 6i; (2*S*)-6-Benzylloxycarbonylamino-2-aminohexanoic Acid 2-Pyridylamide Hydrochloride

To a solution of (2*S*)-6-benzylloxycarbonylamino-2-tert-butoxycarbonylamino-2-aminohexanoic acid 2-pyridylamide (1.48 g, 3.25 mmol) in 25 mL of dioxane is added 5 mL of 4 M hydrogen chloride in dioxane. The reaction mixture is stirred overnight and concentrated to afford 1.54 g (>100% crude) of (2*S*)-6-benzylloxycarbonylamino-2-aminohexanoic acid 2-pyridylamide hydrochloride as a white solid.

¹H NMR (300 MHz, d₆-DMSO) δ 8.50 (m, 1H), 8.39 (d, 1H), 8.07 (d, 1H), 7.90 (t, 1H), 7.35 (s, 5H), 7.21 (t, 1H), 5.00 (s, 2H), 4.70 (bs, 6H), 4.05 (m, 1H), 3.00 (m, 2H), 1.82 (m, 2H), 1.40 (m, 4H) ppm.

25 Example 6; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-[(2*R*)-2-butyl]butanoic Acid [(1*S*)-5-Benzylloxycarbonylamino-1-(2-pyridylcarbonyl)-1-pentyl]amide

To a solution of (2*S*)-6-benzylloxycarbonylamino-2-aminohexanoic acid 2-pyridylamide hydrochloride (0.280 g, 0.660 mmol) in DMF (2 mL) is added triethylamine (0.30 mL, 2.0 mmol), a catalytic amount of HOBt, and pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-butyl)butanoate (0.250 g, 0.55 mmol). The reaction mixture is warmed to 50 °C overnight, poured into water (10 mL) and extracted with two 15 - mL portions of EtOAc. The organic extracts are washed with two 10 - mL portions of 0.1 N hydrochloric acid, two 10 - mL portions of 1 M aqueous sodium carbonate, and saturated aqueous sodium chloride. Drying over sodium sulfate and concentration under reduced pressure followed by purification by chromatography on silica gel (elution with 50% EtOAc - hexanes followed by EtOAc) affords 0.210 g of the crude product which is dissolved in 10 mL of acetic acid and allowed to stand overnight.

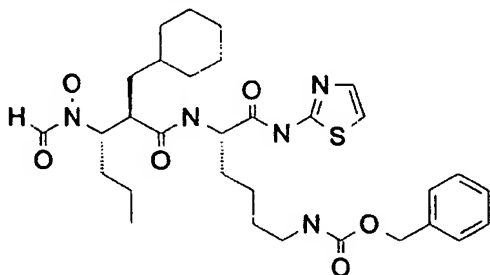
Concentration with ethanol under reduced pressure affords 0.140 g (77%) of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-[(2*R*)-2-butyl]butanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide as a white foam.

¹H NMR (300 MHz, d₆-DMSO) δ 10.40 (bs, 1H), 9.81 and 9.43 (two s, 1H), 8.32 (d, 1H), 8.26 and 8.03 (two s, 1H), 8.20 (t, 1H), 8.05 (d, 1H), 7.78 (t, 1H), 7.36 (m, 5H), 7.25 (t, 1H), 7.11 (t, 1H), 5.01 (s, 2H), 4.52 and 4.02 (two m, 2H), 3.00 (d, 2H), 2.47 (t, 1H), 2.46 (t, 1H), 1.80-1.22 (m, 8H), 1.11 and 1.03 (two d, 3H), 0.94 (two d, 3H), 0.92 (m, 2H), 0.73 and 0.68 (two t, 3H) ppm.

APCI-MS *m/z* 542 (M+H)⁺, 564 (M+Na)⁺.

Anal. Calcd. for C₂₈H₃₉N₅O₆ · 0.20 H₂O · 0.30 C₂H₅OH: C, 61.44; H, 7.43; N, 12.53. Found: C, 61.55; H, 7.28; N, 12.41.

Example 7: (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1*S*)-5-Benzyloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide



Example 7a: Ethyl (2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxyhexanoate

Diisopropylamine (5.89 mL, 44.9 mmol) is dissolved in 30 mL of anhydrous THF and chilled to 0 °C. *n*-Butyllithium (16.5 mL of a 2.5 M solution in hexanes, 41.2 mmol) is added dropwise over 10 min and the resulting pale yellow solution cooled to -78 °C. A 15 - mL THF solution of ethyl (3*R*)-3-hydroxyhexanoate (3.00 g, 18.7 mmol) is added over 10 min and stirred for 30 min. Cyclohexylmethyl iodide (6.29 g, 28.05 mmol) is dissolved in 20 mL of a 1:1 THF/HMPA solution and added to the dianion at -78 °C dropwise. The resulting solution is allowed to warm slowly to 0 °C over 3 h. After stirring overnight at 4 °C 250 mL of a 5% aqueous citric acid solution is added and the mixture is extracted with two 250 - mL portions of ether. The combined organics are washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The crude product is chromatographed on silica gel (elution with 25% EtOAc - hexanes) to provide ethyl (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxyhexanoate (1.44 g, 30% yield) as an oil.

¹H NMR (300 MHz, CDCl₃) δ 4.15 (q, 2H), 3.65 (m, 1H), 2.60 (m, 1H), 2.40 (d, 1H), 1.96-0.94 (m, 23H) ppm.

Example 7b; Methyl (2*R*,3*R*)-2-Benzyl-3-hydroxyhexanoate

Diisopropylamine (8.61 mL, 65.7 mmol) is dissolved in 40 mL of anhydrous THF and chilled to 0 °C. n-Butyllithium (30.1 mL of a 2.0M solution in hexanes, 60.2 mmol) is added dropwise over 10 min and the resulting pale yellow solution cooled to -78 °C. A 15 - mL THF solution of methyl (3*R*)-3-hydroxyhexanoate (4.00 g, 27.4 mmol) is added over 10 min and stirred for 30 min. Benzyl bromide (3.60 mL, 30.1 mmol) is dissolved in 12 mL of a 1:1 THF/HMPA solution and added at -78 °C dropwise. The resulting solution is allowed to warm slowly to 0 °C over 3h. Aqueous 5% citric acid solution (250 mL) is added and the organics are extracted with two 250 - mL portions of ether. The combined organics are washed with saturated aqueous sodium chloride. Drying over sodium sulfate and concentration is followed by which is chromatography on silica gel (elution with 25% EtOAc - hexanes) giving methyl (2*R*,3*R*)-2-benzyl-3-hydroxyhexanoate as an oil (3.03 g, 64% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.30 (m, 2H), 7.18 (m, 3H), 3.65 (m, 1H), 3.62 (s, 3H), 3.02 (m, 2H), 2.75 (m, 1H), 2.55 (d, 1H), 1.50-1.35 (m, 4H), 0.90 (t, 3H) ppm.

Example 7c; Methyl (2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxyhexanoate

Methyl (2*R*,3*R*)-2-benzyl-3-hydroxyhexanoate (3.35 g, 14.2 mmol) is dissolved in 35 mL of MeOH. Under an argon atmosphere 1.00 g of 5% rhodium on carbon is added. The reaction vessel is evacuated and refilled with hydrogen several times and then pressurized with hydrogen to 65 psi. After 8 h the reaction vessel is evacuated and refilled with nitrogen. The solution is filtered and the filtrate concentrated *in vacuo* giving methyl (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxyhexanoate as a clear oil (3.44 g, 99% yield). ¹H NMR (300 MHz, CDCl₃) δ 3.72 (s, 3H), 3.65 (m, 1H), 2.60 (m, 1H), 2.40 (d, 1H), 1.96-0.94 (m, 23H) ppm.

Example 7d; (2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxyhexanoic Acid

Methyl (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxyhexanoate (3.44 g, 14.2 mmol) is dissolved in 3:1:1 THF - MeOH - H₂O (35 mL). To this is added lithium hydroxide monohydrate (1.79 g, 42.6 mmol). The reaction mixture is stirred for 18 h at 25 °C and the mixture is then extracted with ether. The aqueous layer is acidified with solid sodium bisulfate and then extracted with two 250 - mL portions of ether. The

combined organics are washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated under reduced pressure to afford (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxyhexanoic acid as an off-white solid (3.05 g, 96% yield).
¹H NMR (300 MHz, CDCl₃) δ 3.67 (m, 1H), 2.60 (m, 1H), 1.85-0.94 (m, 20H) ppm.

5

Example 7e; (2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxyhexanoic Acid 2-Tetrahydropyranyloxyamide

(2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxyhexanoic acid (3.00 g, 13.1 mmol) is dissolved in 30 mL of anhydrous dichloromethane. EDC (2.77 g, 14.5 mmol) is added followed by 2-tetrahydropyranyloxyamine (3.08 g, 26.3 mmol). The reaction is stirred at 25 °C for 8 h and is then poured into 200 mL of 1 M hydrochloric acid. The mixture is extracted with two 250 - mL portions of dichloromethane. The combined organics are then washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated under reduced pressure to afford (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxyhexanoic acid 2-tetrahydropyranyloxyamide as a foam (3.60 g, 84% yield).

15

¹H NMR (300 MHz, CDCl₃) δ 8.45 (two s, 1H), 4.96 (two s, 1H), 3.95 (m, 1H), 3.64 (m, 2H), 2.75 (two d, 1H), 2.20 (m, 1H), 1.83-0.92 (m, 26H) ppm.

20

Example 7f; (3*R*,4*S*)-3-Cyclohexylmethyl-4-propyl-1-(2-tetrahydropyranyloxy)azetidin-2-one

(2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxyhexanoic acid 2-tetrahydropyranyloxyamide (3.60 g, 11.0 mmol) is dissolved in 15 mL of pyridine and cooled to 0 °C. Methanesulfonyl chloride (0.98 mL, 12.6 mmol) is added dropwise and the reaction is stirred at 0 °C for 6 h. The reaction is poured into 20 mL of ice cold 2 M hydrochloric acid and the mixture extracted with two 25 - mL portions of EtOAc. The combined organics are washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated under reduced pressure to afford the methanesulfonate which is used with no further purification (4.00 g, 90% yield).
¹H NMR (300 MHz, CDCl₃) δ 8.34 and 8.27 (two s, 1H), 4.95 (m, 1H), 4.77 (m, 1H), 3.94 (m, 1H), 3.64 (m, 1H), 3.01 (s, 3H), 2.55 (m, 1H), 1.85-0.95 (m, 26H) ppm.

30

Potassium carbonate (4.09 g, 29.6 mmol) is added to 30 mL of acetone and the suspension is refluxed for 1 h. The above crude methanesulfonate (4.00 g, 9.86 mmol) is dissolved in 10 mL acetone and added. The resulting thick slurry continued to reflux for 16 h and is then cooled to 25 °C. The mixture is filtered and the filtrate is

35

concentrated under reduced pressure giving (3*R*,4*S*)-3-cyclohexylmethyl-4-propyl-1-(2-tetrahydropyranyloxy)azetidin-2-one as an oil (2.28 g, 75% yield).

¹H NMR (300 MHz, CDCl₃) δ 5.18 and 5.01 (two s, 1H), 4.23 and 4.14 (two m, 1H), 3.90 (m, 1H), 3.63 (m, 1H), 3.02 (m, 1H), 1.85-0.93 (m, 26H) ppm.

5

Example 7g; (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic Acid

(3*R*,4*S*)-3-Cyclohexylmethyl-4-propyl-1-(2-tetrahydropyranyloxy)azetidin-2-one (2.25 g, 7.27 mmol) is dissolved in 10 mL of 1,4-dioxane. 2.5 N Aqueous sodium hydroxide solution (8.73 mL, 21.8 mmol) is added and the reaction stirred for 18 h at 25 °C. The solution is diluted with 50 mL of ether and shaken. The organic phase is discarded and the aqueous layer is acidified with solid sodium bisulfate and then extracted with two 25 - mL portions of ether. The combined organic phases are dried over sodium sulfate and concentrated *in vacuo* giving (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic acid as an oil (2.02 g, 85% yield).

15

¹H NMR (300 MHz, CDCl₃) δ 4.84 and 4.74 (two s, 1H), 4.02 and 3.94 (two m, 1H), 3.60 (m, 1H), 3.16-3.03 and 2.91 (two m, 2H), 21.84-0.86 (m, 26H) ppm.

20

Example 7h; Pentafluorophenyl (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoate

(2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic acid (2.00 g, 6.11 mmol) is dissolved in 15 mL of pyridine. Formic acetic anhydride (1.08 mL, 12.2 mmol) is added at 25 °C. The reaction is stirred for an additional 6 h and then is poured into 50 mL of cold 1 M hydrochloric acid. The organics are extracted with two 250 - mL portions of dichloromethane. The combined organic phases are then washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated *in vacuo* to afford (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic acid (2.17 g, 100% yield).

30

APCI-MS *m/z* 378 (M+Na)⁺, 354 (M-H)⁻.

The above formamide (2.17 g, 6.10 mmol) is stirred in dichloromethane and pyridine (0.54 mL, 6.71 mmol) is added. Pentafluorophenyl trifluoroacetate (1.15 mL, 6.71 mmol) is added and the reaction is stirred at 25 °C for 18 h. The reaction mixture is poured into 50 mL of 1 M hydrochloric acid and the mixture is extracted with two

35

250 - mL portions of dichloromethane. The combined organics are washed with 10% aqueous sodium carbonate, dried over sodium sulfate, and concentrated *in vacuo* to afford the crude product. Chromatography on silica gel (elution with 10% EtOAc - hexanes) gives pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoate as a clear viscous oil (2.48 g, 78% yield).
¹H NMR (300 MHz, CDCl₃) δ 8.56 and 8.02 (two d, 1H), 5.03 and 4.83 (two m, 1H), 4.56-4.43 (m, 1H), 4.00 (m, 1H), 3.60 (m, 1H), 3.27-3.06 (m, 1H), 2.03-0.85 (m, 26H) ppm.

Example 7i; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1*S*)-5-Benzylloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide

Pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoate (0.20 g, 0.38 mmol) is dissolved in 5 mL of anhydrous DMF. To this solution is added HOBt (.005 g, 0.04 mmol) followed by (2*S*)-6-benzylloxycarbonylamino-2-aminohexanoic acid 1,3-thiazol-2-ylamide (0.17 g, 0.46 mmol). The reaction is heated at 50 °C for 16 h. The mixture is cooled to 25 °C, diluted with 1:1 hexanes - EtOAc, and washed with 10% aqueous sodium carbonate, 1 M hydrochloric acid, and saturated aqueous sodium chloride. The organics are dried over sodium sulfate, concentrated *in vacuo*, and chromatographed on silica gel (elution with 50% EtOAc - hexanes) giving (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic acid [(1*S*)-5-benzylloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide as white solid (0.19 g, 72% yield).
ESI-MS *m/z* 722 (M+H)⁺.

Example 7; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1*S*)-5-Benzylloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide

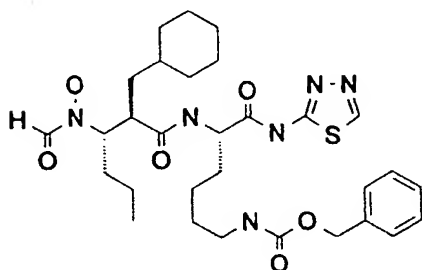
(2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic acid [(1*S*)-5-benzylloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide (0.19 g, 0.27 mmol) is dissolved in 2 mL of 80% acetic acid and stirred overnight at 45 °C. After cooling to 25 °C 2 mL of water is added and the product is filtered to give (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic acid [(1*S*)-5-benzylloxycarbonylamino-1-(1,3-thiazol-2-ylcarbamoyl)-1-pentyl]amide as a white solid (0.15 g, 89% yield).

¹H NMR (300 MHz, CD₃OD) δ 8.36 and 7.95 (two s, 1H), 7.42 (d, 1H), 7.32 (m, 5H), 7.10 (d, 1H), 5.05 (s, 2H), 4.61 (m, 1H), 4.35 and 3.58 (two dt, 1H), 3.12 (t, 2H), 2.89-2.79 (m, 1H), 1.93-0.76 (m, 26H) ppm.

ESI-MS m/z 638 (M+Na)⁺.

- 5 Anal. Calcd. for C₃₁H₄₅N₅SO₆: C, 60.47; H, 7.37; N, 11.37. Found: C, 60.72; H, 7.24; N, 11.13.

Example 8; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic acid [(1*S*)-5-Benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide



10

Example 8a; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1*S*)-5-Benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide

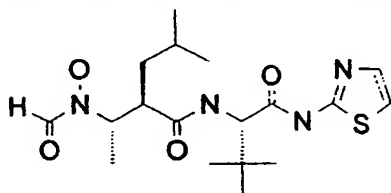
- 15 Pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoate (0.20 g, 0.38 mmol) is dissolved in 5 mL of anhydrous DMF. To this solution is added HOBt (0.05 g, 0.04 mmol) followed by (2*S*)-6-benzyloxycarbonylamino-2-aminohexanoic acid 1,3,4-thiadiazol-2-ylamide (0.17 g, 0.46 mmol). The reaction is heated at 50 °C for 16 h. The mixture is cooled to 25 °C,
- 20 diluted with 1:1 hexanes - EtOAc, and is washed with 10% aqueous sodium carbonate, 1 M hydrochloric acid, and saturated aqueous sodium chloride. The organics are dried over sodium sulfate, concentrated *in vacuo*, and chromatographed on silica gel (elution with 50% EtOAc - hexanes) giving (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide as white
- 25 solid (0.19 g, 72% yield).
ESI-MS m/z 722 (M+H)⁺.

Example 8; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic Acid [(1*S*)-5-Benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide

30

- (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)hexanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide (0.19 g, 0.27 mmol) is dissolved in 2 mL of 80% aqueous acetic acid and is stirred overnight at 45 °C. After cooling to 25 °C 2 mL of water is added and the product is filtered to give (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(cyclohexylmethyl)hexanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(1,3,4-thiadiazol-2-ylcarbamoyl)-1-pentyl]amide as white solid (0.15 g, 89% yield). ¹H NMR (300 MHz, CDCl₃) δ 9.03 (s, 1H), 8.36 and 7.94 (two s, 1H), 7.31 (m, 5H), 5.04 (m, 2H), 4.61 (m, 1H), 4.34 and 3.57 (two dt, 1H), 3.12 (t, 2H), 2.87-2.79 (m, 1H), 1.93-0.79 (m, 26H) ppm. ESI-MS *m/z* 639 (M+Na)⁺, 615 (M-H)⁻. Anal. Calcd. for C₃₀H₄₄N₆SO₆: C, 58.42; H, 7.19; N, 13.63. Found: C, 58.89; H, 7.23; N, 13.89.

- 15 **Example 9;** (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide



Example 9a; Methyl (2*R*,3*R*)-2-(2-Methyl-2-propen-1-yl)-3-hydroxybutanoate

- 20 A solution of 37.7 g (372 mmol) of diisopropylamine in 300 mL of dry THF is cooled to -40 °C and treated with 186.2 mL (372 mmol) of 2.0 M *n*-butyllithium in hexanes. The mixture is stirred at 0 °C for 15 min. The solution is then cooled to -78 °C and treated dropwise with 20 g (170 mmol) of methyl (3*R*)-3-hydroxybutyrate. This solution is stirred at 0 °C for 45 min, followed by stirring at -78 °C for 15 min.
- 25 The flask is charged with 25.5 g (342 mmol) of 3-bromo-2-methyl-1-propene along with 15 mL of HMPA and stirred for 4 h at -78 °C. The reaction mixture then is allowed to stand at -20 °C for 19 h. The reaction is slowly treated with excess saturated aqueous ammonium chloride over 15 min and the resulting solution is partitioned between ether and 1 N aqueous hydrochloric acid. The organics are dried
- 30 over magnesium sulfate and concentrated *in vacuo* to afford 23.1 g of crude oil. A sample (10 g) of the crude product is chromatographed on silica gel (elution with 4:1 hexanes - EtOAc) to afford 8.1 g (28%) of methyl (2*R*,3*R*)-2-(2-methyl-3-propen-1-yl)-3-hydroxybutanoate as an oil.

¹H NMR (400 MHz, CDCl₃) δ 4.77 (d, 2H), 3.90 (m, 1H), 3.69 (s, 3H), 2.68 (m, 1H), 2.52-2.41 (m, 2H), 2.36 (m, 1H), 1.5 (s, 3H), 1.22 (s, 3H) ppm.

APCI-MS m/z 173 (M+H)⁺.

5 Example 9b; Methyl (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxybutanoate

Methyl (2*R*,3*R*)-2-(2-methyl-2-propen-1-yl)-3-hydroxybutanoate (8.1 g, 47.1 mmol) in 85 mL of EtOAc is treated with 800 mg of 10% palladium on carbon and the mixture is evacuated and purged with nitrogen. The heterogeneous solution is stirred under 52 psi of hydrogen for a period of 1.5 h. Filtration and concentration of the filtrate *in vacuo* affords 7.99 g (96%) of methyl (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxybutanoate as an oil.

¹H NMR (400 MHz, CDCl₃) δ 3.85 (m, 1H), 3.69 (s, 3H), 2.51-2.42 (m, 2H), 1.71-1.62 (m, 1H), 1.58-1.48 (m, 1H), 1.38-1.30 (m, 1H), 1.22 (d, 3H), 0.94-0.86 (dd, 6H) ppm.

APCI-MS m/z 175 (M+H)⁺.

Example 9c; (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxybutanoic Acid

Methyl (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxybutanoate (7.99 g, 46 mmol) in 50 mL of THF is treated with 50 mL of water containing 3.9 g (92 mmol) of lithium hydroxide monohydrate. The reaction flask is treated with 5.0 mL of MeOH and allowed to stir for 17 h at 25 °C. The mixture is partitioned between water and ether followed by separation of the aqueous layer. The aqueous solution is brought to pH 3 with 6 N aqueous hydrochloric acid and the mixture is extracted with ether. The organic phase is dried over magnesium sulfate and concentrated under reduced pressure to afford 6.6 g (90%) of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxybutanoic acid.

¹H NMR (400 MHz, CDCl₃) δ 3.91 (m, 1H), 2.50 (m, 1H), 1.75-1.61 (m, 2H), 1.40-1.29 (m, 1H), 1.29-1.24 (d, 3H), 0.96 (dd, 6H) ppm.

APCI-MS m/z 161 (M+H)⁺.

Example 9d; (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxyhexanoic Acid 2-Tetrahydropyranyloxyamide

(2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxybutanoic acid (6.6 g, 41.2 mmol) and 5.3 g (45.3 mmol) of 2-tetrahydropyranyloxyamine are stirred in 60 mL of

dichloromethane as 8.7 g (45.3 mmol) of EDC is added. After 4 h at 25 °C the reaction mixture is partitioned between 1 N aqueous hydrochloric acid and dichloromethane and the organics are washed with saturated aqueous sodium bicarbonate. The organics are dried over magnesium sulfate and concentrated under reduced pressure to afford 5.9 g (55%) of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxyhexanoic acid 2-tetrahydropyranyloxyamide as an oil.

¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, 1H), 5.0 (d, 1H), 3.81-4.00 (m, 2H), 2.05-2.15 (m, 1H), 1.45-1.83 (m, 10H), 1.23-1.38 (m, 1H), 1.22 (d, 3H), 0.96 (dd, 6H) ppm.

APCI-MS m/z 260 (M+H)⁺.

Example 9e; (3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-methyl-1-(2-tetrahydropyranyloxy)azetidin-2-one

(2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxyhexanoic acid 2-tetrahydropyranyloxyamide (5.8 g, 22.3 mmol) in 42 mL of dry pyridine is cooled to 0 °C and treated with 2.81 g (24.6 mmol) of methanesulfonyl chloride followed by stirring at 0 °C for 4 h. The reaction mixture is poured into 1 N aqueous hydrochloric acid and extracted with EtOAc. The organics are washed with three portions of saturated aqueous cupric sulfate. The organic layer is dried over magnesium sulfate and concentrated under reduced pressure to provide 6.1 g of the crude methanesulfonate which is used directly in the next step.

The crude methanesulfonate is stirred in 150 mL of dry acetone and treated with 7.5 g (54.3 mmol) of potassium carbonate. The reaction is stirred at reflux for 17 h and the mixture is then allowed to cool to 25 °C. The mixture is filtered and the filtrate is concentrated to afford an oil (4.5 g) which is chromatographed on silica gel (elution with 4:1 hexanes - EtOAc) to give 3.5 g (65%) of (3*R*,4*S*)-3-(2-methyl-1-propyl)-4-methyl-1-(2-tetrahydropyranyloxy)azetidin-2-one as an oil.

¹H NMR (400 MHz, CDCl₃) δ 5.10 and 4.97 (two m, 1H), 4.18-3.97 (m, 2H), 3.60 (m, 1H), 3.03-2.88 (m, 1H), 1.82-1.50 (m, 8H), 1.30-1.25 (m, 1H), 1.24-1.20 (dd, 3H), 0.95 (dd, 6H) ppm.

APCI-MS m/z 242 (M+H)⁺.

Example 9f; (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoic Acid

(3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-methyl-1-(2-tetrahydropyranyloxy)azetidin-2-one (3.5 g, 14.5 mol) in 30 mL of ethylene glycol dimethyl ether is treated with 20

mL of 2.5 M aqueous sodium hydroxide solution. The mixture is stirred at 25 °C for 16 h and is then brought to pH 3 by addition of saturated aqueous sodium bisulfate solution. The mixture is extracted with ether and the organics are dried over magnesium sulfate and concentrated under reduced pressure to give 3.2 g (84%) of (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoic acid as an oil.

¹H NMR (400 MHz, CDCl₃) δ 4.82 and 4.74 (two m, 1H), 4.00-3.83 (m, 1H), 3.60-3.50 (m, 1H), 3.33-3.20 (m, 1H), 3.00-2.96 (m, 1H), 1.82-1.40 (m, 8H), 1.20-1.08 (m, 1H), 1.11-1.05 (dd, 3H), 0.93 (dd, 6H) ppm.

APCI-MS m/z 260 (M+H)⁺.

Example 9g; Pentafluorophenyl (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoate

To 25 mL of anhydrous pyridine is added 3.2 g (12.3 mmol) of (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoic acid and the mixture is cooled to 0 °C as 3.3 g (37 mmol) of formic acetic anhydride is added. The mixture is stirred at 0 °C for 2 h. The solution is then concentrated *in vacuo* to dryness and the residue is treated with 50 mL of EtOAc, 2.5 g (12.5 mmol) of dicyclohexylcarbodiimide, 2.2 g (12 mmol) of pentafluorophenol, and 1.7 mL (12 mmol) of triethylamine. The resulting reaction mixture is stirred at 25 °C for 16 h followed by concentration *in vacuo*. The crude oil is chromatographed on silica gel (elution with 4:1 hexanes - EtOAc) to afford 3.5 g (63%) of pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoate as an oil.

¹H NMR (400 MHz, CDCl₃) δ 8.48 (s, 1H), 4.85 (m, 1H), 4.70-4.59 (m, 1H), 4.06-3.83 (m, 1H), 3.63-3.59 (m, 1H), 3.27-3.03 (m, 1H), 1.96-1.20 (m, 12H), 1.00-0.95 (dd, 6H) ppm.

APCI-MS m/z 454 (M+H)⁺.

Example 9h; (2*S*)-2-tert-Butoxycarbonylamino-3,3-dimethylbutanoic Acid 1,3-thiazol-2-ylamide

A solution of 10.0 g (76.2 mmol) of (2*S*)-2-amino-3,3-dimethylbutanoic acid in 100 mL of THF and 50 mL of water is treated at 25 °C with 20 mL (100 mmol) of 5 N aqueous sodium hydroxide followed by 20 g (91.6 mmol) of di-tert-butyl dicarbonate. The mixture is stirred vigorously at 25 °C for 24 h. The mixture is

- chilled to 0 °C and is treated dropwise with saturated aqueous sodium bisulfate solution to adjust the reaction mixture to pH 2. The mixture is extracted with two 200 - mL portions of EtOAc. The combined organic phases are dried over magnesium sulfate and concentrated *in vacuo* to afford 18.5 g of crude (2*S*)-2-tert-butoxycarbonylamino-3,3-dimethylbutanoic acid. The crude acid is stirred in 200 mL of DMF at 0 °C as 12.3 g (91.1 mmol) of HOBt, 30 mL (273 mmol) of NMM, and 17.5 g (91.2 mmol) of EDC are added in turn. After 30 min at 0 °C 9.1 g (90.1 mmol) of 2-amino-1,3-thiazole is added. The mixture is stirred at 0 °C for 30 min and at 50 °C for 2 h. The mixture is then concentrated *in vacuo* and the residue is diluted with 250 mL of EtOAc. The organic phase is washed with water, saturated aqueous sodium chloride, is dried over magnesium sulfate, and concentrated *in vacuo*. Chromatography on silica gel (elution with 30% EtOAc - hexanes followed by 70% EtOAc - hexanes) affords 20.1 g (84%) of (2*S*)-2-tert-butoxycarbonylamino-3,3-dimethylbutanoic acid 1,3-thiazol-2-ylamide as an oil.
- ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, 1H), 7.03 (d, 1H), 5.42 (bd, 1H), 3.41 (s, 1H), 1.43 (s, 9H), 1.12 (s, 9H) ppm.

Example 9i; (2*S*)-2-Amino-3,3-dimethylbutanoic Acid 1,3-Thiazol-2-ylamide

- A solution of 18.3 g (58.4 mmol) of (2*S*)-2-tert-butoxycarbonylamino-3,3-dimethylbutanoic acid 1,3-thiazol-2-ylamide in 50 mL of dichloromethane is treated dropwise at 25 °C with 50 mL of TFA. After 4 h at 25 °C the mixture is concentrated *in vacuo* and the residue is diluted with 20 mL of dichloromethane. The mixture is stirred at 0 °C as saturated aqueous sodium carbonate is added dropwise to bring the mixture to pH 8. The mixture is diluted with water to a volume of 200 mL and the solid product is collected and dried *in vacuo* affording 11.6 g (93%) of (2*S*)-2-amino-3,3-dimethylbutanoic acid 1,3-thiazol-2-ylamide.
- ¹H NMR (300 MHz, CDCl₃) δ 7.50 (d, 1H), 7.01 (d, 1H), 3.42 (s, 1H), 1.62 (bs, 2H), 1.11 (s, 9H) ppm.
- ESI-MS *m/z* 236 (M+Na)⁺, *m/z* 212 (M-H)⁻.

Example 9; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

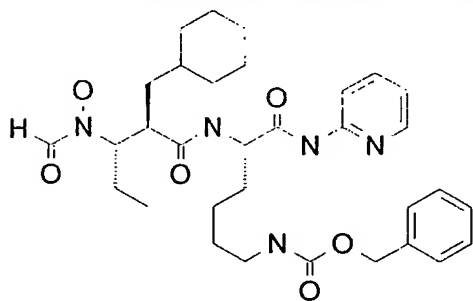
- Pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoate (1.0 g, 2.2 mmol) and 0.517 g (2.4 mmol) of (2*S*)-2-amino-3,3-dimethylbutanoic acid 1,3-thiazol-2-ylamide in 15 mL of DMF are treated

with 0.338 mL (2.4 mmol) of triethylamine. The reaction is stirred at 50 °C for 16 h followed by concentration *in vacuo*. The crude product is chromatographed on silica gel (elution with 99:1:0.1 dichloromethane - MeOH - 30% aqueous ammonium hydroxide) to afford (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as an oil.

The above 2-tetrahydropyranyloxyamine is dissolved in 80% acetic acid and heated at 40 °C for 17 h. The solution is then allowed to cool to 25 °C and is concentrated to dryness affording a solid, which is treated with toluene and the mixture is concentrated *in vacuo*. This toluene treatment and concentration is repeated several times. The resulting solid is triturated with ether and the solid is collected and dried to afford 92 mg (10%) of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide.

¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 1H), 7.53 (d, 1H), 7.18 (d, 1H), 7.02 (d, 1H), 4.88 (d, 1H), 4.08-4.00 (m, 1H), 2.90-2.82 (m, 1H), 1.65-1.54 (m, 1H), 1.46-1.32 (m, 3H), 1.31-1.04 (m, 11H), 0.82 (dd, 3H), 0.72 (dd, 3H) ppm.
APCI-MS *m/z* 399 (M+H)⁺.

Example 10; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)pentanoic Acid [(1*S*)-5-Benzoyloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide



Example 10a; Methyl (2*R*,3*R*)-2-Benzyl-3-hydroxypentanoate

A solution of diisopropylamine (10.6 mL, 81.1 mmol) in 35 mL of anhydrous THF is cooled to -45 °C. *n*-Butyllithium (32.4 mL, 2.5 M solution in hexanes) is added dropwise over 10 minutes. A solution of methyl (3*R*)-3-hydroxypentanoate (5.1 g, 38.6 mmol) in 5 mL of anhydrous THF is added dropwise and the mixture is stirred at -45 °C for 45 min. Benzyl bromide (7.90 g, 46.3 mmol) is dissolved in 5 mL of anhydrous THF - DMPU (1:1) and added to the reaction mixture. Stirring is continued at -45 °C for 1 h, then at -20 °C for 18 h. After warming to 25 °C, the

reaction mixture is extracted with ether. The ether extracts are washed with 1 N hydrochloric acid, water, saturated aqueous sodium chloride, and dried over sodium sulfate. The solvent is removed under vacuum and the resulting yellow oil is purified by chromatography on silica gel (elution with hexanes - EtOAc) to give 4.67 g (54%) of methyl (2*R*,3*R*)-2-benzyl-3-hydroxypentanoate as a light yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.30 (m, 2H), 7.25 (m, 3H), 3.65 (s, 3H), 3.60 (m, 1H), 3.05 (m, 2H), 2.8 (m, 1H), 2.65 (d, 1H), 1.55 (m, 2H), 1.0 (t, 3H) ppm.

APCI-MS m/z 223 (M+H)⁺.

10 Example 10b; Methyl (2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxypentanoate

Methyl (2*R*,3*R*)-2-benzyl-3-hydroxypentanoate (4.60 g, 20.7 mmol) is dissolved in 8 mL of MeOH in a pressure vessel. 5% Rhodium on alumina (0.25 g) is added, and the system is evacuated and flushed with nitrogen, evacuated again and filled with 50 psi of hydrogen. After 5 d, the hydrogenation is 90 % complete by ¹H NMR analysis. The reaction mixture is filtered, the filtrate is concentrated under vacuum, and the residue is purified by chromatography on silica gel (elution with hexanes - EtOAc) to give 2.49 g (53%) of methyl (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxypentanoate as a colorless oil.

15 ¹H NMR (300 MHz, CDCl₃) δ 3.75 (s, 3H), 3.55 (m, 1H), 2.65 (m, 1H), 2.45 (d, 1H), 1.9-0.95 (m, 18H) ppm.

APCI-MS m/z 229 (M+H)⁺.

Example 10c; (2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxypentanoic Acid

25

A solution of lithium hydroxide (0.29 g, 12.0 mmol) is added to a solution of methyl (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxypentanoate (2.49 g, 10.9 mmol) in 30 mL of THF and 10 mL of MeOH. The mixture is stirred at 25 °C for 18 h, acidified to pH 2 with concentrated hydrochloric acid and extracted with EtOAc. The EtOAc layer is washed with water, saturated aqueous sodium chloride, dried over sodium sulfate and the solvent is evaporated under vacuum to give 2.2 g (95%) of (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxypentanoic acid as a white solid.

30 ¹H NMR (300 MHz, CDCl₃) δ 3.60 (m, 1H), 2.65 (m, 1H), 1.9 (d, 1H), 1.80-0.80 (m, 18H) ppm.

35 APCI-MS m/z 213 (M-H)⁻.

Example 10d; (2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxypentanoic Acid 2-Tetrahydropyranyloxyamide

2-Tetrahydropyranyloxyamine (2.50 g, 21.8 mmol) and EDC (2.70g, 14.2 mmol) is added to a solution of (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxypentanoic acid in 30 mL of dichloromethane. The resulting solution is stirred at 25 °C for 2 h and is diluted with dichloromethane. The organic phase is washed with aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and dried over sodium sulfate. After evaporating the solvent under vacuum, the residue is purified by chromatography on silica gel with hexanes - EtOAc to give 2.84 g (83%) of (2*R*,3*R*)-2-cyclohexylmethyl-3-hydroxypentanoic acid 2-tetrahydropyranyloxyamide as a white solid.
¹H NMR (400 MHz, CDCl₃) δ 8.90 (m, 1H), 4.95 (m, 1H), 4.00 (m, 1H), 3.60 (m, 2H), 3.05 (m, 1H), 2.25 (m, 1H), 1.95-0.80 (m, 24H) ppm.
APCI-MS m/z 312 (M-H).

Example 10e; (3*R*,4*S*)-3-Cyclohexylmethyl-4-ethyl-1-(2-tetrahydropyranyloxy)azetidin-2-one

(2*R*,3*R*)-2-Cyclohexylmethyl-3-hydroxypentanoic acid 2-tetrahydropyranyloxyamide (2.84 g, 9.1 mmol) is dissolved in 20 mL of anhydrous pyridine and cooled to 0 °C. Methanesulfonyl chloride (0.8 mL, 9.9 mmol) is added. After 2 h at 0 °C, the reaction mixture is poured into 1 N hydrochloric acid and extracted with EtOAc. The organic layer is washed with saturated cupric sulfate, water, saturated aqueous sodium chloride, and dried over sodium sulfate. The solvent is evaporated under vacuum to give the crude methanesulfonate as a brown oil which is dissolved in 20 mL of acetone and added to a suspension of potassium carbonate (3.8 g, 27.3 mmol) in 50 mL of refluxing acetone. The mixture is kept at reflux for 18 h, cooled to 25 °C, and filtered. The filtrate is evaporated under vacuum, and the resulting brown oil is purified by chromatography on silica gel with hexanes - EtOAc to give 1.85 g (69%) of (3*R*,4*S*)-3-cyclohexylmethyl-4-ethyl-1-(2-tetrahydropyranyloxy)azetidin-2-one as a yellow oil.
¹H NMR (400 MHz, CDCl₃) δ 5.15 and 5.0 (two s, 1H), 4.2 (m, 1H), 3.8 (m, 1H), 3.65 (m, 1H), 3.05 (m, 1H), 1.90-0.80 (m, 26H) ppm.
APCI-MS m/z 296 (M+H)⁺.

Example 10f; (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoic Acid

A mixture of (3*R*,4*S*)-3-cyclohexylmethyl-4-ethyl-1-(2-tetrahydropyranyloxy)azetidin-2-one (1.85 g, 6.3 mmol), 10 mL of 5 M aqueous sodium hydroxide, 25 mL of THF and 20 mL of MeOH is stirred at 25 °C for 20 h.

- 5 The mixture is acidified with saturated aqueous sodium bisulfate and the mixture is extracted with EtOAc. The organic layer is washed with water, saturated aqueous sodium chloride, and dried over sodium sulfate. The solvent is evaporated under vacuum to give 1.92 g (98%) of (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoic acid as a yellow oil.
- 10 ¹H NMR (400 MHz, CDCl₃) δ 4.85 and 4.80 (two s, 1H), 3.90 (m, 1H), 3.60 (m, 1H), 3.0 (m, 2H), 1.90-0.80 (m, 24H) ppm.
- APCI-MS *m/z* 313 (M)⁺.

- Example 10g; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoic Acid
- 15

- A solution of (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoic acid (1.90 g, 6.1 mmol) in 20 mL of anhydrous pyridine is cooled to 0 °C. Formic acetic anhydride (1.6 g, 18.2 mmol) is added. The cooling bath is removed and the mixture is stirred at 25 °C for one hour. Pyridine is evaporated under vacuum, the residue is dissolved in EtOAc and washed with saturated aqueous cupric sulfate, water, saturated aqueous sodium chloride, and dried over sodium sulfate. The solvent is evaporated under vacuum to give an oil which is purified by chromatography on silica gel with hexanes - EtOAc to give 1.34 g (64%) of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoic acid as a colorless oil.
- 20
- ¹H NMR (300 MHz, CDCl₃) δ 8.6 and 8.05 (two s, 1H), 5.1 and 4.85 (two s, 1H), 4.3 (m, 1H), 4.0 (m, 1H), 3.6-3.4 (m, 1H), 3.0-2.7 (m, 1H), 2.0-0.9 (m, 23H) ppm.
- 25 APCI-MS *m/z* 340 (M-H)⁻.

- 30
- Example 10h; Pentafluorophenyl (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoate

- 4-Methylmorpholine (0.85 mL, 7.8 mmol), EDC (0.97 g, 5.1 mmol) and pentafluorophenol (1.43 g, 7.8 mmol) are added to a solution of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoic acid in 20 mL of dichloromethane. After stirring for one hour at 25 °C, the reaction mixture is diluted
- 35

with dichloromethane and washed with aqueous sodium bisulfate, saturated aqueous sodium bicarbonate and water, and dried over sodium sulfate. The solvent is evaporated under vacuum and the residue is purified by chromatography on silica gel with hexanes - EtOAc to give 1.20 g (61%) of pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoate as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 8.60 and 8.05 (two d, 1H), 5.10 and 4.90 (two m, 1H), 4.40 (m, 1H), 4.0 (m, 1H), 3.65 (m, 1H), 3.30 and 3.10 (two m, 1H), 2.10-0.90 (m, 24H) ppm.

APCI-MS *m/z* 508 (M+H)⁺, 530 (M+Na)⁺.

Example 10i; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoic Acid [(1*S*)-5-Benzylloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide

4-Methylmorpholine (0.53 mL, 4.8 mmol), 1-hydroxybenzotriazole (0.16 g, 1.2 mmol) and (2*S*)-6-benzylloxycarbonylamino-2-aminohexanoic acid 2-pyridylamide hydrochloride is added to a solution of pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoate (0.60 g, 1.2 mmol) in 20 mL of DMF. The mixture is heated at 60 °C for 18 h. DMF is evaporated under vacuum, the residue is dissolved in EtOAc and washed with aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, the solvent is evaporated and the residue is purified by chromatography on silica gel (elution with 1:1 hexanes - EtOAc) to give 0.41 g (50%) of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoic acid [(1*S*)-5-benzylloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 8.85 (br m, 1H), 8.50 and 8.0 (two s, 1H), 8.3 (m, 1H), 8.10 (d, 1H), 7.70 (t, 1H), 7.35 (m, 5H), 7.05 (m, 1H), 6.60 (br m, 1H), 5.2-4.8 (m, 4H), 4.65 (m, 1H), 4.0 (m, 1H), 3.60 (m, 1H), 3.2 (m, 2H), 2.0-0.70 (m, 32H) ppm.

APCI-MS *m/z* 680 (M+H)⁺, 702 (M+Na)⁺.

Example 10; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(cyclohexylmethyl)pentanoic Acid [(1*S*)-5-Benzylloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide

A solution of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(cyclohexylmethyl)pentanoic acid [(1*S*)-5-benzylloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide (0.41 g, 0.6 mmol) in 15 mL of 80% aqueous

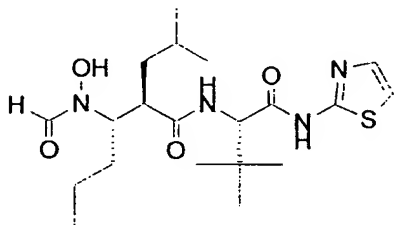
acetic acid is heated at 50 °C for one h. The solvent is evaporated under vacuum. The residue is dissolved in toluene and evaporated to dryness. The resulting solid is kept under vacuum at 25 °C for 24 h, then triturated with ether, recrystallized from dichloromethane - MeOH - ether, and dried under vacuum at 60 °C to give 0.197 g of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(cyclohexylmethyl)pentanoic acid [(1*S*)-5-benzyloxycarbonylamino-1-(2-pyridylcarbamoyl)-1-pentyl]amide as a solid.

¹H NMR (300 MHz, CDCl₃) δ 8.40 and 7.95 (two s, 1H), 8.75 (d, 1H), 8.10 (d, 1H), 7.70 (t, 1H), 7.30 (m, 5H), 7.10 (t, 1H), 5.05 (s, 2H), 4.55 (m, 1H), 3.45 (m, 1H), 3.10 (m, 2H), 2.80 (m, 1H), 2.0-0.75 (m, 24H) ppm.

APCI-MS *m/z* 618 (M+Na)⁺, 596 (M+H)⁺.

Anal. Calcd. for C₃₂H₄₅N₅O₆ · 0.25 C₂H₄O₂: C, 63.93; H, 7.54; N, 11.47. Found: C, 63.86; H, 7.44; N, 11.27.

Example 35; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide



Example 35a; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

To a solution of pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoate (450 mg, 0.936 mmol) in DMF (5 mL) is added (2*S*)-2-amino-3,3-dimethylbutanoic acid 1,3-thiazol-2-ylamide hydrochloride (347 mg, 1.40 mmol), NMM (236 mg, 2.34 mmol) and HOBt (10 mg, 0.074 mmol). The resulting solution is heated to 50 °C and stirred for 20 h then poured into 50 mL of 1:1 EtOAc – hexanes and washed sequentially with 1 M aqueous HCl, 1 M aqueous sodium carbonate solution and brine. The organic layer is dried over anhydrous magnesium sulfate, concentrated, and purified by silica gel chromatography (1:1 EtOAc - hexanes) to provide 241 mg of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as a foam.

¹H NMR (400 MHz, CDCl₃) δ 8.44 and 8.06 (two s, 1H), 7.82 and 7.74 (two d, 1H), 7.08 (d, 1H), 6.64 (bs, 1H), 4.98 (m, 1H), 4.82 (m, 1H), 4.20-3.88 (m, 2H), 3.82, 2.82 and 2.66 (three m, 1H), 3.56 (m, 1H), 1.98-1.48 (m, 10H), 1.42-1.14 (m, 3H), 1.06 (m, 9H), 0.92-0.62 (m, 9H) ppm.

5 ESI-MS m/z 533 (M+Na)⁺.

Example 35; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

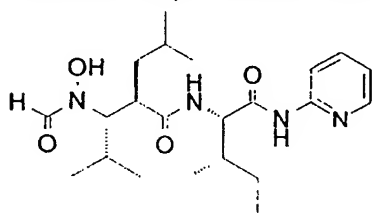
10 A solution of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)hexanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide (240 mg, 0.473 mmol) in acetic acid - water (4:1 v/v, 1 mL) is heated to 50 °C for 16 h. The reaction mixture is concentrated, then twice dissolved in toluene and concentrated. The crude product is recrystallized from dichloromethane - MeOH
15 - ether to provide 141 mg of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)hexanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 8.36 and 7.95 (two s, 1H), 7.42 (d, 1H), 7.09 (d, 1H), 4.56 (s, 1H), 4.35 and 3.58 (two dt, 1H), 2.97 and 2.86 (two dt, 1H), 1.82 (m, 1H),
20 1.58-1.22 (m, 5H), 1.18 (m, 1H), 1.06 (s, 9H), 0.87 (m, 6H), 0.76 (t, 3H) ppm.

ESI-MS m/z 449.4 (M+Na)⁺.

Anal. Calcd. for C₂₀H₃₄N₄O₄S: C, 56.31; H, 8.03; N, 13.13. Found: C, 56.27; H, 7.95; N, 13.17.

25 Example 76; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1*S*,2*S*)-2-Methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide



Example 76a; Methyl (3*S*)-3-Hydroxy-4-methylpentanoate

30 Methyl isobutyrylacetate (135 g, 0.935 mol) in 135 mL of degassed MeOH is treated with 564 mg of [(RuCl₂)(PhI)(*R*-(+)-BINAP)]. The solution is purged with nitrogen and stirred under 62 psi of hydrogen while heating at 100 °C for 72 h. The reaction mixture is cooled to 25 °C and degassed followed by purging with nitrogen.

The reaction mixture is concentrated to dryness and the residue is distilled (39 °C, 0.52 mm Hg) to afford 106 g of methyl (3*S*)-3-hydroxy-4-methylpentanoate as an oil. ¹H NMR (400 MHz, CDCl₃) δ 3.80 (m, 1H), 3.70 (s, 3H), 2.82 (s, 1H), 2.52-2.40 (m, 2H), 1.70 (m, 1H), 0.97 (dd, 6H) ppm.

5 ESI-MS m/z 147 (M+H)⁺.

Example 76b; Methyl (2*R*,3*R*)-2-(2-Methyl-2-propene-1-yl)-3-hydroxy-4-methylpentanoate

10 Diisopropylamine (22.9 g, 227 mmol) in 350 mL of THF is chilled to -20 °C as 90.6 mL (227 mmol) of 2.5 M n-butyllithium is added. The mixture is stirred at 0 °C for 15 min and is cooled to -45 °C. Methyl-(3*S*)-3-hydroxy-4-methyl-pentanoate (15 g, 103 mmol) is added and the reaction is allowed to stir for 1 h at -78 °C. The reaction mixture is treated with 20.8 g (154 mmol) of 3-bromo-2-methyl-1-propene
15 and 15 mL of HMPA. After 18 h at 4 °C the mixture is concentrated to dryness and the residue is slurried in water and is acidified to pH 5 with 12 N HCl. The mixture is extracted with ether and the organic layer is washed with saturated sodium chloride. The organic phase is dried over magnesium sulfate, concentrated, and the residue is chromatographed on silica gel (20% EtOAc - hexanes) to yield 11.1 g of methyl
20 (2*R*,3*R*)-2-(2-methyl-2-propene-1-yl)-3-hydroxy-4-methylpentanoate as an oil. ¹H NMR (400 MHz, CDCl₃) δ 4.78 (d, 2H), 4.10 (m, 1H), 3.65 (s, 3H), 3.33 (m, 1H), 2.59 (m, 1H), 2.50-2.25 (m, 2H), 1.73 (s, 3H), 1.65 (m, 1H), 0.95 (dd, 6H) ppm. ESI-MS m/z 201 (M+H)⁺.

25 Example 76c; Methyl (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-4-methylpentanoate

Methyl (2*R*,3*R*)-2-(2-methyl-2-propene-1-yl)-3-hydroxy-4-methylpentanoate (11.1 g, 55 mmol) in 100 mL of EtOAc is treated with 200 mg of 10% palladium on charcoal. The reaction mixture is evacuated and purged with nitrogen gas followed by
30 stirring under 65 psi of hydrogen. After 24 h the mixture is filtered and and concentrated to dryness affording 11.0 g of methyl (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxy-4-methylpentanoate. ¹H NMR (400 MHz, CDCl₃) δ 3.70 (s, 3H), 3.30 (m, 1H), 2.70 (m, 1H), 2.50 (d, 1H), 1.78-1.37 (m, 3H), 0.95 (m, 12H) ppm.
35 ESI-MS m/z 203 (M+H)⁺.

Example 76d; (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-4-methylpentanoic Acid

Methyl (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxy-4-methylpentanoate (11.0 g, 54 mmol) in 110 mL of THF and 21 mL of MeOH is treated with 110 mL of 2.5 N aqueous sodium hydroxide. The reaction stirred at 25 °C for 4 h and concentrated to half its volume. The mixture is extracted with ether. The aqueous phase is made acidic (pH 3) and is extracted with ether. The ether phase is dried over magnesium sulfate and concentrated to afford 7.6 g of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxy-4-methylpentanoic acid as a solid.

¹H NMR (400 MHz, CDCl₃) δ 3.37 (m, 1H), 2.75 (m, 1H), 1.80-1.60 (m, 3H), 1.42 (m, 1H), 0.98 (m, 12H) ppm.

ESI-MS *m/z* 189 (M+H)⁺.

Example 76d; (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-4-methylpentanoic Acid 2-Tetrahydropyranyloxyamide

(2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-4-methylpentanoic acid (7.5 g, 40 mmol) in 75 mL of acetonitrile is treated with 5.9 g (44 mmol) of HOBt, 5.2 g (44 mmol) of 2-tetrahydropyranyloxyamine, and 8.4 g (44 mmol) of EDC. After stirring at 25 °C for

17 h the mixture is concentrated to dryness. The reaction mixture is partitioned between saturated sodium bicarbonate and methylene chloride. The organic phase is dried over magnesium sulfate and concentrated to afford 8.2 g of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxy-4-methylpentanoic acid 2-tetrahydropyranyloxyamide. The product is used without further purification.

Example 76e; (3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-isopropyl-1-(2-tetrahydropyranyloxy)azetidin-2-one

(2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-4-methylpentanoic Acid 2-tetrahydropyranyloxyamide (8.2 g, 28.5 mol) in 115 ml of pyridine is cooled to 0-5 °C and treated with 3.6 g (31.4 mmol) of methanesulfonyl chloride. After 4 h at 25 °C the mixture is concentrated to dryness. The residue is taken up in 150 mL of acetone and 43.0 g (314 mmol) of potassium carbonate is added. The mixture is stirred at reflux for 18 h, then is filtered and the filtrate is concentrated in vacuo.

Chromatography of the crude product on silica gel (10% EtOAc - hexanes) affords 5.2 g of (3*R*,4*S*)-3-(2-methyl-1-propyl)-4-isopropyl-1-(2-tetrahydropyranyloxy)azetidin-2-one as an oil.

¹H NMR (400 MHz, CDCl₃) δ 5.27 and 5.06 (two s, 1H), 4.30 and 4.07 (two m, 1H), 3.61(m, 2H), 3.02 (m, 1H), 2.00-1.58 (m, 9H), 1.38 (m, 1H), 1.10-0.95 (m, 12H) ppm.
ESI-MS m/z 270 (M+H)⁺.

- 5 Example 76f; (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid

(3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-isopropyl-1-(2-tetrahydropyranyloxy)azetidin-2-one (5.2 g, 19.3 mmol) in 52 mL of THF and 10 mL
10 of MeOH is treated with 52 mL of 2.5 N aqueous sodium hydroxide. After 18 hr at 25 °C the mixture is concentrated to half its volume. The aqueous layer is washed with ether and then is cooled to 0-5 °C, acidified (pH 4) with 12 N HCl, and is extracted with ether. The ether phases are dried over magnesium sulfate and concentrated in vacuo to afford 5.1 g of (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid as an oil.

15 ¹H NMR (400 MHz, CDCl₃) δ 4.83 and 4.78 (two m, 1H), 3.98-3.80 (m, 1H), 3.59 (m, 1H), 3.00 (m, 1H), 2.83 (m, 1H), 2.00-1.40 (m, 9H), 1.20 (m, 1H), 1.10-0.95 (m, 12H) ppm.

ESI-MS m/z 288 (M+H)⁺.

20

Example 76g; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid

(2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid (5.1 g, 17.7 mmol) in 50 mL of pyridine is chilled to 0 °C and
25 treated with 1.1 g (19.5 mmol) of formic acetic anhydride. The reaction is concentrated to dryness after 2 h to afford 5.4 g of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid as an oil, used directly in the next step.

30 ¹H NMR (400 MHz, CDCl₃) δ 8.65 (m, 1H), 8.50 and 8.00 (two s, 1H), 5.05 and 4.90 (two m, 1H), 4.38-4.16 (m, 1H), 3.97 (m, 1H), 3.60 (m, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.20-1.98 (m, 2H), 1.90-1.10 (m, 7H), 1.05-0.80 (m, 12H) ppm.

ESI-MS m/z 316 (M+H)⁺.

- 35 Example 76h: (1*S*,2*S*)-2-Methyl-1-(pyridin-2-ylcarbamoyl)-1-butylamine Dihydrochloride

- A solution of 300 g (1.3 mol) of (2*S*,3*S*)-2-(tert-butoxycarbonylamino)-3-methylpentanoic acid (N-BOC-L-isoleucine) is stirred at 0 °C in 1 L of dichloromethane as 270 g (163 mol) of carbonyldiimidazole is added over 30 min. After 1 h at 0 °C 125 g (1.32 mol) of 2-aminopyridine is added and the mixture is stirred at 25 °C for 48 h. Water (200 mL) is added and the dichloromethane is removed *in vacuo*. The residue is treated with saturated aqueous sodium bisulfate to pH 4. The solid slurry is filtered and dried under suction. The collected solid is slurried in 1 L of MeOH as 500 mL of 12 N hydrochloric acid is added. After 2 h the mixture is concentrated to dryness and the solid is recrystallized from hot 3:1 MeOH-isopropanol to afford 122 g of (1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butylamine dihydrochloride as a white solid.
- ¹H NMR (300 MHz, CD₃OD) δ 8.50 (d, 1H), 8.44 (t, 1H), 7.86 (d, 1H), 7.67 (t, 1H), 4.19 (d, 1H), 2.20 (m, 1H), 1.71 (m, 1H), 1.33 (m, 1H), 1.20 (d, 3H), 1.05 (t, 3H) ppm.
- Anal. Calcd. for C₁₁H₁₇N₃O · 2HCl: C, 47.15; H, 6.84; N, 15.00. Found: C, 47.08; H, 6.85; N, 14.93.

- (1*S*,2*S*)-2-Methyl-1-(pyridin-2-ylcarbamoyl)-1-butylamine dihydrochloride (1.1 g, 3.92 mmol) is shaken in 20 mL of dichloromethane with 7 mL of 10% aqueous sodium carbonate. Separation and concentration of the organic phase affords 701 mg of (1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butylamine as an oil which is used without further purification.

- Example 76i; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1*S*,2*S*)-2-Methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide

- (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid (200 mg, 0.634 mmol) in 20 mL of DMF is treated with 188 mg (1.4 mmol) of HOBt, 0.64 mL of triethylamine, and 617 mg (1.4 mmol) of BOP. The mixture is stirred at 0-5 °C for 15 min and 145 mg (0.697 mmol) of (1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butylamine is added. The mixture is stirred at 25 °C for 17 h and is then concentrated to dryness. The resulting oil is partitioned between EtOAc and saturated sodium bicarbonate. The organics are dried over magnesium sulfate, concentrated, and the residue is chromatographed on silica gel (elution with 50% EtOAc - hexanes) to give 165 mg of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid [(1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide as an oil.

^1H NMR (400 MHz, CDCl_3) δ 8.70-8.40 (m, 2H), 8.30-8.10 (d, 1H), 7.86 (m, 1H), 7.20 (m, 1H), 6.80-6.55 (m, 1H), 5.80-5.60 (m, 1H), 5.30-5.10 (m, 1H), 4.70 (m, 1H), 4.50-4.05 (m, 1H), 3.90-3.70 (m, 2H), 2.30-1.70 (m, 4H), 1.69-1.66 (dd, 3H), 1.60-1.30 (m, 2H), 1.29-1.20 (dd, 3H), 1.25-0.95 (m, 20H) ppm.

5 ESI-MS m/z 505 ($M+H$) $^+$.

Example 76; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1*S*,2*S*)-2-Methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide

10 (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid [(1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide (165 mg, 0.327 mmol) in 10 ml of 80% acetic acid is allowed to stir at 40 °C for 17 h and is concentrated to dryness. The resulting solid is treated with toluene and concentrated *in vacuo*. Treatment of the residue with ether and collection of the

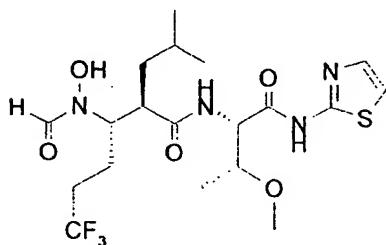
15 resulting white solid affords 110 mg of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid [(1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide.

^1H NMR (400 MHz, d_6 -acetone) δ 9.47 (s, 1H), 8.70-8.40 (s, 1H), 8.50 (s, 1H), 8.27 (d, 1H), 8.18 (d, 1H), 7.80 (m, 2H), 7.08 (m, 1H), 4.61 (m, 1H), 3.65 (m, 1H), 3.30-3.10 (m, 1H), 2.00 (m, 1H), 1.70-1.45 (m, 2H), 1.40-1.20 (m, 1H), 1.10 (m, 5H), 1.05 (m, 4H), 0.95 (m, 10H), 0.75 (m, 2H) ppm.

ESI-MS m/z 421 ($M+H$) $^+$.

Example 77; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1*S*,2*R*)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

25



Example 77a; 4,4,4-Trifluorobutanoic Acid

30

Ethyl 4,4,4-trifluorobutanoate (120 g, 706 mmol), THF (120 mL), 3 N aqueous NaOH (500 mL, 1.5 mol) and 43 mL of MeOH are mixed and allowed to stir

at 25 °C for a total of 17 hr. The reaction is concentrated to dryness and extracted with ether. The aqueous phase is made acidic (pH 3) using 12 N HCl and is extracted with ether. The organic phase is concentrated to afford 58 g of 4,4,4-trifluorobutanoic acid as a solid.

- 5 ¹H NMR (400MHz, CDCl₃) δ 2.85 (m, 2H), 2.65 (m, 2H), 10.5 (s, 1H) ppm.
ESI-MS m/z 143 (M+H)⁺.

Example 77b; 4,4,4-Trifluorobutanoyl Chloride

- 10 4,4,4-Trifluorobutanoic acid (61 g, 429 mmol) in 650 mL of methylene chloride is cooled to 0-5 °C. To this mixture is added dropwise 136 g (1.07 mol) of oxalyl chloride and 3.0 mL of DMF. The reaction is allowed to warm to 25 °C and is stirred for 18 h. The reaction is concentrated to half its volume and is treated with ether and magnesium sulfate. The mixture is filtered and the volatiles are allowed to
15 evaporate at 50 °C. The resulting volatile acid chloride (40 g) isolated as an oil is used directly.

¹H NMR (400 MHz, CDCl₃) δ 3.20 (m, 2H), 2.58 (m, 2H) ppm.

Example 77c; Methyl 6,6,6-Trifluoro-3-oxohexanoate

- 20 4,4,4-Trifluoromethylbutanoyl chloride (40 g, 249 mmol), 400 mL of dichloromethane and 35.9 g (249 mmol) of 2,2-dimethyl-1,3-dioxane-4,6-dione are mixed and cooled to 0-5 °C. Pyridine (100 mL) is added and the mixture is stirred for 18 h at 25 °C. The reaction mixture is concentrated to dryness and the resulting red
25 oil is dissolved in 200 mL of MeOH. The mixture is heated at reflux for a total of 2 hr and is concentrated to dryness. The reaction product is distilled (30 °C, 49 mm Hg) to afford 23 g of methyl 6,6,6-trifluoro-3-oxohexanoate as an oil.

¹H NMR (400 MHz, CDCl₃) δ 3.78 (s, 3H), 3.5 (s, 2H), 2.83 (m, 2H), 2.43 (m, 2H) ppm.

- 30 ESI-MS m/z 199 (M+H)⁺.

Example 77d; Methyl (3R)-3-Hydroxy-6,6,6-trifluorohexanoate

- 35 Methyl 6,6,6-trifluoro-3-oxohexanoate (23 g, 116 mmol), 46 mL of degassed MeOH and 231 mg of [(RuCl₂(PhH)(R-(+)-BINAP)] are mixed in a pressure bottle and the mixture is stirred under 72 psi of hydrogen gas at 100 °C for 20 h. The reaction mixture is cooled to 25 °C and purged with nitrogen gas. The reaction

mixture is concentrated to dryness and the residue distilled (39 °C, 0.52 mm Hg) to afford 21.1 g of methyl (3*R*)-3-hydroxy-6,6,6-trifluorohexanoate as an oil.

¹H NMR (400 MHz, CDCl₃) δ 4.05 (m, 1H), 3.75 (s, 3H), 3.15 (m, 1H), 2.49-2.05 (m, 4H), 1.70 (m, 2H) ppm.

5 ESI-MS m/z 201 (M+H)⁺.

Example 77e; Methyl (2*R*,3*R*)-2-(2-Methyl-2-propen-1-yl)-3-hydroxy-6,6,6-trifluorohexanoate

10 A solution of 11.1 g (110 mmol) of diisopropylamine in 200 mL of THF is chilled to -20 °C as 44 mL of n-butyllithium (110 mmol, 2.5 M solution in hexanes) is added dropwise. The solution stirred at 0 °C for a 15 minutes and is cooled to -45 °C.

Methyl (3*R*)-3-hydroxy-6,6,6-trifluorohexanoate (10 g, 50 mmol) is added and the reaction is allowed to stir for 1 h at -78 °C. The reaction mixture is treated with 7.5 g
15 (55 mmol) of 3-bromo-2-methyl-1-propene and 1.0 mL of HMPA. The reaction is stirred at 4 °C for a total of 18 h followed by concentrating to dryness. The residue is treated with water and made acidic (pH 5) using 12 N HCl. The mixture is extracted with ether and the organic layer is washed with saturated aqueous sodium chloride.

The organic phase is dried over magnesium sulfate, concentrated *in vacuo*, and the
20 residue is chromatographed on silica gel (elution with 20% EtOAc - hexanes) to yield 10 g of methyl (2*R*,3*R*)-2-(2-methyl-2-propen-1-yl)-3-hydroxy-6,6,6-trifluorohexanoate as an oil.

¹H NMR (400 MHz, CDCl₃) δ 4.79 (d, 2H), 3.71 (s, 3H), 3.68 (m, 1H), 2.88 (dd, 1H), 2.67 (m, 1H), 2.50-2.32 (m, 3H), 2.17 (m, 1H), 1.74 (s, 3H), 1.80-1.58 (m, 2H) ppm.

25 ESI-MS m/z 255 (M+H)⁺.

Example 77f; Methyl (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoate

30 Methyl (2*R*,3*R*)-2-(2-methyl-2-propen-1-yl)-3-hydroxy-6,6,6-trifluorohexanoate (10 g, 39 mmol) is taken up in 100ml of EtOAc and 500 mg of Pd(OH)₂ is added. The reaction mixture is evacuated and purged with nitrogen gas followed by stirring under 62 psi of hydrogen for 16 h at 25 °C. The reaction mixture is filtered and the filtrate is concentrated *in vacuo* to afford 9.7 g of methyl (2*R*,3*R*)-2-
35 (2-methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoate as an oil.

¹H NMR (400 MHz, CDCl₃) δ 3.73 (s, 3H), 3.65 (m, 1H), 2.50 (m, 1H), 2.48-2.30 (m, 2H), 2.23-2.07 (m, 1H), 1.70-1.67 (m, 2H), 1.65-1.50 (m, 2H), 1.43-1.37 (m, 1H), 0.96 (dd, 6H) ppm.

ESI-MS m/z 257 (M+H)⁺.

5

Example 77g; (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoic Acid

Methyl (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoate
10 (9.7 g, 40 mmol) in 100 mL of THF and 21 mL of MeOH is treated with 100 mL (250 mmol) of 2.5 N aqueous sodium hydroxide. The reaction is stirred at 25 °C for 17 h and is concentrated to half its volume. The mixture is extracted with ether. The aqueous phase is made acidic (pH 3) and is extracted with ether. The ether phase is dried over magnesium sulfate and is concentrated to dryness to afford 4.1 g of
15 (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoic acid as an oil.
¹H NMR (400 MHz, CDCl₃) δ 3.78 (m, 1H), 2.55 (m, 1H), 2.50-2.35 (m, 1H), 2.34-2.18 (m, 1H), 1.80-1.69 (m, 1H), 1.78-1.53 (m, 3H), 1.35-1.27 (m, 1H), 0.90 (dd, 6H) ppm.

ESI-MS m/z 243 (M+H)⁺.

20

Example 77h: (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoic Acid 2-Tetrahydropyranyloxyamide

(2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoic acid (4.1 g,
25 17 mmol) and 2.2 g (19 mmol) of 2-tetrahydropyranyloxyamine in 50 mL of acetonitrile is treated with 4.2 g (19 mmol) of HOBt and 3.6 g (19 mmol) of EDC. The reaction mixture is stirred at 25 °C for a total of 17 h and is concentrated to dryness. The reaction mixture is partitioned between saturated sodium bicarbonate and dichloromethane. The organic phase is dried over magnesium sulfate and
30 concentrated to dryness to yield 4.9 g of (2*R*,3*R*)-2-(2-methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoic acid 2-tetrahydropyranyloxyamide as an oil, used without further purification.

ESI-MS m/z 243 (M+H)⁺.

35 Example 77i; (3*R*,4*S*)-3-(2-Methyl-1-propyl)-4-(3,3,3-trifluoropropyl)-1-(2-tetrahydropyranyloxy)azetidin-2-one

- (2*R*,3*R*)-2-(2-Methyl-1-propyl)-3-hydroxy-6,6,6-trifluorohexanoic acid 2-tetrahydropyranyloxyamide (4.9 g, 14 mmol) in 50 mL of pyridine is cooled to 0-5 °C and treated with 2.5 g (22 mmol) of methanesulfonyl chloride. After 4 h at 25 °C the mixture is concentrated to dryness. The resulting oil is taken up in 100 mL of acetone and treated with 19.9 g (144 mmol) of potassium carbonate. The reaction is stirred at reflux for 18 h, is filtered, and the filtrate is concentrated *in vacuo*. The crude product is chromatographed on silica gel (elution with 10% EtOAc - hexanes) to afford 1.1 g of (3*R*,4*S*)-3-(2-methyl-1-propyl)-4-(3,3,3-trifluoropropyl)-1-(2-tetrahydropyranyloxy)azetidin-2-one as an oil.
- ¹H NMR (400 MHz, CDCl₃) δ 5.10 and 4.98 (two s, 1H), 4.20-3.88 (m, 2H), 3.60 (m, 1H), 3.10 (m, 1H), 2.5-2.10 (m, 2H), 2.0 (m, 8H), 1.37-1.20 (m, 1H), 0.95 (dd, 6H) ppm.
- ESI-MS *m/z* 324 (M+H)⁺.

- Example 77j; (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid

- (3*R*,4*S*)-3-(2-methyl-1-propyl)-4-(3,3,3-trifluoropropyl)-1-(2-tetrahydropyranyloxy)azetidin-2-one (1.1 g, 3.4 mmol) in 25 mL of THF is treated with 25 mL (62.5 mmol) of 2.5 N aqueous NaOH and 6.0 mL of MeOH. The reaction mixture is stirred at 25 °C for 18 h and concentrated to half its volume. The aqueous is extracted with ether, then the aqueous phase is cooled to 0-5 °C, acidified (pH 4) and is extracted with ether. The organic phase is dried over magnesium sulfate and concentrated to afford 981 mg of (2*R*,3*S*)-3-(2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid as an oil. The reaction product is used without further purification.
- ESI-MS *m/z* 342 (M+H)⁺.

- Example 77k; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid

- (2*R*,3*S*)-3-(2-Tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid (981 mg, 2.9 mmol) in 10 mL of pyridine is cooled to 0-5 °C and treated with 1.28 g (14.5 mmol) of formic acetic anhydride. After 2 h at 0 °C the mixture is concentrated *in vacuo* to afford 1.0 g of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid. The reaction product is used without purification.
- ESI-MS *m/z* 370 (M+H)⁺.

Example 77l; (2*S*,3*R*)-2-tert-Butoxycarbonylamino-3-methoxybutanoic Acid 1,3-Thiazol-2-ylamide

- 5 To a solution of (2*S*,3*R*)-2-tert-butoxycarbonylamino-3-methoxybutanoic acid (0.20 g, 0.86 mmol) and 2-aminothiazole (0.095 g, 0.95 mmol) in anhydrous DMF (2.0 mL) at 25 °C is added anhydrous DIEA (0.30 mL, 1.7 mmol) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-3-oxo[4,5-*b*]pyridinium hexafluorophosphate (HATU) (0.33 g, 0.86 mmol). The mixture is stirred at for 18 h
10 and then is diluted with 30 mL of dichloromethane and 50 mL of water. The aqueous phase is extracted with dichloromethane and the dichloromethane extracts are washed with 10% aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. The solvent is removed under vacuum and the residue is purified by chromatography on silica gel (elution with 2:1 EtOAc -
15 hexanes) to give 0.23 g of (2*S*,3*R*)-2-tert-butoxycarbonylamino-3-methoxybutanoic acid 1,3-thiazol-2-ylamide as a white solid.
¹H NMR (300 MHz, CDCl₃) δ 9.93 (s, 1H), 7.51 (d, 1H), 7.04 (d, 1H), 5.51 (d, 1H), 4.52 (d, 1H), 4.09 (m, 1H), 3.45 (s, 3H), 1.65 (s, 9H), 1.22 (d, 3H) ppm.

- 20 Example 77m; (1*S*,2*R*)-1-(1,3-Thiazol-2-ylcarbonyl)-2-methoxy-1-propylamine Hydrochloride

- To a solution of (2*S*,3*R*)-2-tert-butoxycarbonylamino-3-methoxybutanoic acid 1,3-thiazol-2-ylamide (0.22 g, 0.70 mmol) in 2.5 mL dichloromethane at 25 °C is
25 added 1.5 mL (6 mmol) of 4 N hydrogen chloride in dioxane. The reaction mixture is stirred for 2 h and the resulting white precipitate is isolated by filtration to give 0.20 g of (1*S*,2*R*)-1-(1,3-thiazol-2-ylcarbonyl)-2-methoxy-1-propylamine hydrochloride as a white solid.
¹H NMR (300 MHz, CD₃OD) δ 7.57 (d, 1H), 7.33 (d, 1H), 4.13 (d, 1H), 3.93 (m, 1H),
30 3.44 (s, 3H), 1.37 (d, 3H) ppm.

- Example 77n; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1*S*,2*R*)-2-Methoxy-1-(1,3-thiazol-2-ylcarbonyl)-1-propyl]amide

- 35 (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid (200 mg, 0.541 mmol) in 10 mL of DMF is treated with

264 mg (0.596 mmol) of BOP, 80 mg (0.596 mmol) of HOBT, and 0.6 g (5.96 mmol) of TEA. After 15 min at 0-5 °C the mixture is treated with 150 mg (0.596 mol) of (1*S*,2*R*)-1-(1,3-thiazol-2-ylcarbamoyl)-2-methoxy-1-propylamine hydrochloride.

After 17 h at 25 °C the mixture is concentrated to dryness and the residue is

- 5 partitioned between EtOAc and saturated sodium bicarbonate. The organics are dried over magnesium sulfate, concentrated *in vacuo* and the residue is chromatographed on silica gel (elution with 50% EtOAc – hexanes) to give 237 mg of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid [(1*S*,2*R*)-2-methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as an oil.
- 10 ESI-MS *m/z* 567 (M+H)⁺.

Example 77; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1*S*,2*R*)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

15

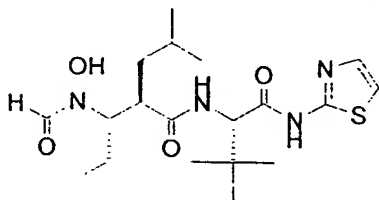
(2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid [(1*S*,2*R*)-2-methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide (237 mg, 0.418 mmol) is stirred in 20 mL of 80% acetic acid for 17 h at 40 °C. The mixture is concentrated *in vacuo*. Toluene is added to the mixture and

20 concentration is repeated. Ether is added and the resulting white solid is collected to afford 108 mg of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid [(1*S*,2*R*)-2-methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide.

¹H NMR (400 MHz, d₆-acetone) δ 9.10 (s, 1H), 8.5 (s, 1H), 8.10 (s, 1H), 7.92-7.80 (d, 1H), 7.42 (d, 1H), 7.17 (d, 1H), 4.90-5.00 (m, 1H), 4.45 (m, 1H), 3.35 (s, 3H), 3.20-3.00 (m, 1H), 2.25-2.00 (m, 3H), 1.90-1.50 (m, 3H), 1.30-1.10 (m, 4H), 0.95 (d, 3H), 0.80 (d, 3H) ppm.

ESI-MS *m/z* 483 (M+H)⁺.

- 30 Example 78; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide



Example 78a; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

5 To a solution of pentafluorophenyl (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoate (340 mg, 0.728 mmol) in DMF (3.6 mL) is added (2*S*)-2-amino-3,3-dimethylbutanoic acid 1,3-thiazol-2-ylamide hydrochloride (270 mg, 1.09 mmol), NMM (184 mg, 1.82 mmol) and HOBt (10 mg, 0.074 mmol). The resulting solution is heated to 50 °C and stirred for 20 h
10 then poured into 50 mL of 1:1 EtOAc – hexanes and washed sequentially with 1 M aqueous HCl, saturated sodium bicarbonate solution and brine. The organic layer is dried over anhydrous magnesium sulfate, concentrated, and purified by silica gel chromatography (1:1 EtOAc - hexanes) to provide (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as a foam (161 mg, 45% yield).
15 ESI-MS *m/z* 519.3 (M+Na)⁺.

Example 78; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

20

A solution of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)pentanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide (160 mg, 0.325 mmol) in acetic acid - water (4:1 v/v, 1 mL) is heated to 50 °C for 16 h. The reaction mixture is concentrated, then twice dissolved in toluene
25 and concentrated. The crude product is recrystallized from dichloromethane - MeOH - ether to provide (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)pentanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as a white solid (115 mg, 86% yield).

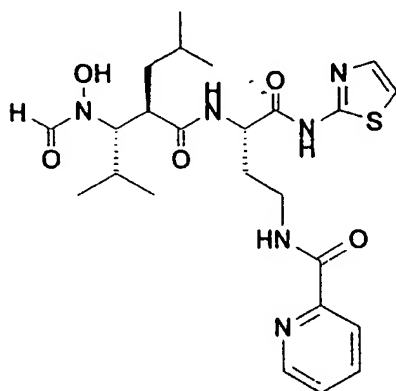
¹H NMR (400 MHz, CD₃OD) δ 8.40 and 7.96 (two s, 1H), 7.42 (d, 1H), 7.09 (d, 1H),
30 4.55 (s, 1H), 4.25 and 3.46 (two dt, 1H), 2.96 and 2.88 (two dt, 1H), 1.82 (m, 1H), 1.58-1.30 (m, 3H), 1.16 (m, 1H), 1.06 (s, 9H), 0.86 (m, 6H), 0.76 (t, 3H) ppm.

ESI-MS *m/z* 435 (M+Na)⁺.

Anal. Calcd. for C₁₉H₃₂N₄O₄S: C, 55.32; H, 7.82; N, 13.58. Found: C, 55.04; H, 7.87; N, 13.43.

35

Example 79; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1*S*)-3-(2-Pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide



- 5 **Example 79a;** (2*S*)-4-(2-Pyridylcarbonylamino)-2-tert-butoxycarbonylaminobutanoic Acid 1,3-Thiazol-2-ylamide

To a solution of 0.592 g (4.81 mmol) of picolinic acid in 30 mL of dichloromethane at 0 °C is added 0.780 g (4.81 mmol) of carbonyldiimidazole. After
 10 20 min at 25 °C 1.0 g (4.58 mmol) of (2*S*)-4-amino-2-tert-butoxycarbonylaminobutanoic acid is added and the mixture is stirred 18 h. The mixture is concentrated under reduced pressure and the residue is taken up in 30 mL of dichloromethane and 0.780 g (4.81 mmol) of carbonyldiimidazole is added. After
 15 15 min 0.505 g (5.04 mmol) of 2-aminothiazole is added and the mixture is stirred for 6 h at 25 °C. The mixture is then concentrated *in vacuo* and the residue is chromatographed on silica gel (elution with 50% EtOAc – hexanes) to provide 1.26 g of (2*S*)-4-(2-pyridylcarbonylamino)-2-tert-butoxycarbonylaminobutanoic acid 1,3-thiazol-2-ylamide as an oil.

¹H NMR (400 MHz, CDCl₃) δ 11.74 (bs, 1H), 8.50 (bs, 2H), 8.20 (d, 1H), 7.79 (t, 1H), 7.45 (d, 1H), 7.40 (t, 1H), 6.90 (d, 1H), 5.81 (m, 1H), 4.49 (bs, 1H), 3.93 (q, 1H), 3.33 (dd, 1H), 2.28 (m, 1H), 2.03 (m, 1H), 1.42 (s, 9H) ppm.

Example 79b; (1*S*)-3-(2-Pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propylamine Hydrochloride

25

(2*S*)-4-(2-pyridylcarbonylamino)-2-tert-butoxycarbonylaminobutanoic acid 1,3-thiazol-2-ylamide (1.26 g, 3.11 mmol) is added to 5 mL of 4 N hydrogen chloride in dioxane. After 3 h the mixture is concentrated *in vacuo* to provide 1.07 g of (1*S*)-3-

(2-pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propylamine hydrochloride as a solid which is used without further purification.

Example 79c; (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1*S*)-3-(2-pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

A solution of 0.110 g (0.349 mmol) of (2*R*,3*S*)-3-formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid in 5 mL of DMF is treated at 25 °C with 0.077 mL (0.697 mmol) of NMM, 57 mg (0.418 mmol) of HOBt, and 80 mg (0.418 mmol) of EDC. After 30 min 158 mg (0.418 mmol) of (1*S*)-3-(2-pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propylamine hydrochloride is added and the mixture is stirred at 25 °C for 18 h. The mixture is diluted with ether and is washed with saturated aqueous sodium chloride. The organics are dried over magnesium sulfate and concentrated *in vacuo*. The crude product is purified by chromatography on silica gel (elution with EtOAc) to provide 70 mg of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid [(1*S*)-3-(2-pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as an oil. ESI-MS *m/z* 625 (*M*+Na)⁺.

Example 79; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic Acid [(1*S*)-3-(2-pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

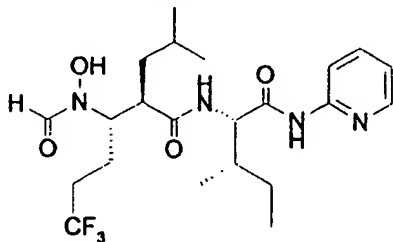
A solution of 70 mg (0.116 mmol) of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid [(1*S*)-3-(2-pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide is stirred in 2 mL of 80% aqueous acetic acid for 18 h. The mixture is concentrated *in vacuo* to a gum. Crystallization of the product from dichloromethane - ether gave 31 mg of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)-4-methylpentanoic acid [(1*S*)-3-(2-pyridylcarbonylamino)-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as a white solid.

¹H NMR (400 MHz, d₆-DMSO) δ 12.19 (s, 1H), 9.59 and 9.37 (two s, 1H), 8.74 (d, 1H), 8.60 (d, 1H), 8.54 (m, 1H), 8.02 (m, 1H), 7.98 (m, 1H), 7.98 and 7.87 (two d, 1H), 7.60 (m, 1H), 7.44 and 7.17 (two d, 1H), 4.60 (bs, 1H), 3.21 (m, 3H), 2.96 (m,

1H), 2.04 (m, 1H), 1.96 (m, 1H), 1.68 (m, 1H), 1.42 (m, 1H), 1.38 (bt, 1H), 0.98 (d, 3H), 0.88 (d, 3H), 0.76 (d, 3H), 0.71 (d, 3H) ppm.

ESI-MS m/z 519 (M+H)⁺, 541 (M+Na)⁺.

- 5 **Example 80;** (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1*S*,2*S*)-2-Methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide



- 10 **Example 80a;** (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1*S*,2*S*)-2-Methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide

- 15 (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid (200 mg, 0.541 mmol) in 20 mL of DMF is treated with 81 mg of HOBT, 0.6 g (0.596 mmol) of TEA, and 264 mg of BOP. The mixture is stirred at 0-5 °C for 15 min and is then treated with 123 mg (0.60 mmol) of (1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butylamine. After 17 h at 25 °C the mixture is concentrated to dryness. The resulting oil is partitioned between EtOAc and saturated sodium bicarbonate. The organic phase is dried over magnesium sulfate,
- 20 concentrated, and the residue is chromatographed on silica gel (elution with 50% EtOAc – hexanes) to give 113 mg of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid [(1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide as an oil.
- ESI-MS m/z 559 (M+H)⁺.

25

Example 80; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1*S*,2*S*)-2-Methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide

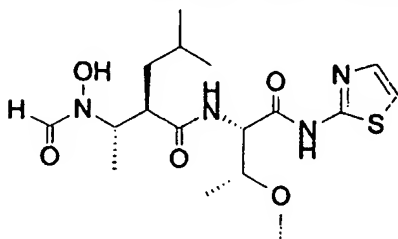
- 30 (2*R*,3*S*)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid [(1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide (113 mg, 0.202 mmol) is stirred in 20 mL of 80% acetic acid for 17 h at 40 °C. The mixture is concentrated to dryness and the residue is treated with toluene and

concentrated. Treatment with ether and collection of the resulting solid affords 43 mg of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid [(1*S*,2*S*)-2-methyl-1-(pyridin-2-ylcarbamoyl)-1-butyl]amide.

¹H NMR (400 MHz, d₆-acetone) δ 9.10-9.20 (s, 1H), 8.30-8.10 (m, 2H), 8.00 (s, 1H), 7.70 (m, 1H), 7.05 (m, 1H), 6.90 (m, 1H), 4.90-4.70 (m, 2H), 3.80 (m, 1H), 2.90 (s, 2H), 3.20-3.00 (m, 20H) ppm.

ESI-MS *m/z* 475 (M+H)⁺.

Example 81; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)butanoic Acid [(1*S*,2*R*)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide



Example 81a; (2*R*,3*S*)-3-Formyl-2-tetrahydropyranyloxyamino-2-(2-methyl-1-propyl)butanoic Acid [(1*S*,2*R*)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

A mixture of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoic acid (0.15 g, 0.52 mmol), BOP (0.29 g, 0.65 mmol), HOBT (88 mg, 0.65 mmol) and NMM (0.33 g, 3.25 mmol) in DMF (8 mL) is stirred at 25 °C under an argon atmosphere for 1 h. (1*S*,2*R*)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-aminopropane hydrochloride (0.16 g, 0.65 mmole) is added and the mixture is stirred at 25 °C for 18 h. The reaction mixture is poured into a mixture of hexanes (100 mL) and EtOAc (100 mL) and the resulting mixture is washed with 1 M aqueous sodium hydrogen sulfate, brine, 1 M aqueous sodium carbonate and brine. The organic phase is dried over sodium sulfate, concentrated *in vacuo* and the residue is purified by column chromatography on silica gel (elution with 3:1 EtOAc – hexanes) to give 0.12 g of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoic acid [(1*S*,2*R*)-2-methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as a white foam.

¹H NMR (300 MHz, CDCl₃) δ 9.99 (s, 1H), 8.50 and 8.35 (two s, 1H), 7.51 (d, 1H), 7.05 (d, 1H), 6.78 (m, 1H), 4.91 (m, 2H), 4.05 (m, 3H), 3.66 (m, 1H), 3.56 (s, 3H),

2.80 (m, 1H), 1.89-1.53 (m, 8H), 1.38-1.28 (m, 4H), 1.17 (d, 3H), 0.98 (d, 3H), 0.93 (dd, 3H) ppm.

ESI-MS m/z 485 (M+H)⁺.

- 5 Example 81; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-butanoic Acid [(1*S*,2*R*)-2-Methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

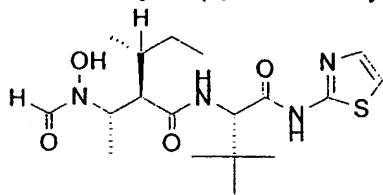
- A mixture of (2*R*,3*S*)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)butanoic acid [(1*S*,2*R*)-2-methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide (0.12 g, 0.24 mmol) in 80% acetic acid (10 mL) is stirred at ambient temperature for 2 d. The mixture is concentrated *in vacuo*, ethanol and water are added to the residue and the mixture is concentrated *in vacuo*. The residue is treated with a mixture of hexanes - ether (4:1) and allowed to stand for 3 h. The resulting solid is filtered, washed with hexanes, and dried to give 77 mg of (2*R*,3*S*)-3-formyl-hydroxyamino-2-(2-methyl-1-propyl)butanoic acid [(1*S*,2*R*)-2-methoxy-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as a white solid.

- ¹H NMR (300 MHz, d₆-DMSO) δ 12.14 (s, 1H), 9.80 and 9.45 (two s, 1H), 8.49 (m, 1H), 8.29 and 8.00 (two s, 1H), 7.50 (d, 1H), 7.24 (d, 1H), 4.72 (t, 1H), 4.29 and 3.77 (two m, 2H), 3.26 (s, 3H), 2.83 (m, 1H), 1.42 (m, 2H), 1.06 (m, 7H), 0.89 (d, 3H), 0.78 (m, 3H) ppm.

ESI-MS m/z 401 (M+H)⁺.

Anal. Calcd. for C₁₇H₂₈N₄O₅S: C, 50.98; H, 7.05; N, 13.99; S, 8.01. Found: C, 50.71; H, 6.99; N, 13.85; S, 7.93.

- 25 Example 82; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-[(2*R*)-2-butyl]butanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide



Example 82a; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-[(2*R*)-2-butyl]butanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

30

A mixture of (2*R*,3*S*)-3-(formyl-tetrahydropyranyloxyamino)-2-[(2*R*)-2-butyl]butanoic acid (0.2 g, 0.7 mmol), DIEA (0.27 g, 2.1 mmol) and (2*S*)-2-amino-3,3-dimethylbutanoic acid 1,3-thiazol-2-ylamide hydrochloride (0.22 g, 0.9 mmol) in DMF (15 mL) is stirred at 25 °C. 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-

triazolo-3-oxo[4,5-b]pyridinium hexafluorophosphate (HATU) (0.27 g, 0.7 mmole) is added and the mixture is stirred at 25 °C for 3 d. The reaction mixture is diluted with EtOAc and washed with 1 M aqueous sodium hydrogen sulfate, brine, 1 M aqueous sodium carbonate and brine. The organic phase is dried over sodium sulfate, concentrated *in vacuo* and the residue is purified by column chromatography on silica gel (elution with 50% EtOAc – hexanes) to give 0.12 g of (2*R*,3*S*)-3-(formyl-tetrahydropyranyloxyamino)-2-[(2*R*)-2-butyl]butanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as a white foam.

¹H NMR (400 MHz, CDCl₃) δ 11.89 (br s, 1H), 8.42-8.13 (m, 1H), 7.75 (d, 1H), 7.03 (d, 1H), 6.60-6.20 (m, 1H), 4.97 (br s, 1H), 4.73 (m, 1H), 4.30 (m, 1H), 4.04 (m, 1H), 3.62 (m, 2H), 2.69 (m, 1H), 1.84-1.50 (m, 8H), 1.45-1.22 (m, 3H), 1.08-0.72 (m, 15H) ppm.

ESI-MS *m/z* 483 (M+H)⁺.

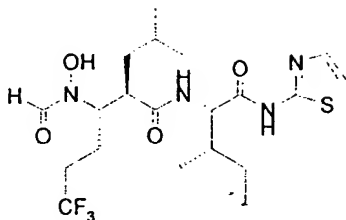
Example 82; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-[(2*R*)-2-butyl]butanoic Acid [(1*S*)-2,2-Dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide

A mixture of (2*R*,3*S*)-3-formyl-tetrahydropyranyloxyamino-2-[(2*R*)-2-butyl]butanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide (0.11 g, 0.23 mmol) in 80% acetic acid (10 mL) is stirred at 25 °C for 24 h, then at 40 °C for 24 h. The mixture is concentrated *in vacuo*, EtOAc is added to the residue and the mixture is concentrated *in vacuo*. The EtOAc treatment is repeated several times concentrating *in vacuo* after each addition. The residue is dissolved in MeOH (4 mL) and water (20 mL) is added. The resulting mixture is lyophilized to give 58 mg of (2*R*,3*S*)-3-(formyl-hydroxyamino)-2-[(2*R*)-2-butyl]butanoic acid [(1*S*)-2,2-dimethyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-propyl]amide as an off-white solid.

¹H NMR (300 MHz, d₆-DMSO) δ 12.24 (s, 1H), 9.84 and 9.52 (two s, 1H), 8.30 and 8.09 (s and m, 2H), 7.54 (d, 1H), 7.27 (d, 1H), 4.62 and 4.11 (two m, 2H), 2.92 (m, 1H), 1.49 (m, 3H), 1.30-0.72 (m, 18H) ppm.

ESI-MS *m/z* 399 (M+H)⁺.

Example 83; (2*R*,3*S*)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1*S*,2*S*)-2-Methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide



Example 83a; (2*S*,3*S*)-2-tert-Butoxycarbonylamino-3-methylpentanoic Acid 1,3-Thiazol-2-ylamide

5

To a solution of (2*S*,3*S*)-2-tert-butoxycarbonylamino-3-methylpentanoic acid (7.0 g, 30.3 mmol) in 60 mL of methylene chloride is added carbonyldiimidazole (4.9 g, 30.3 mmol). After 30 min at 0 °C, 2-amino-1,3-thiazole (6.06 g, 60.6 mmol) is added. The mixture is stirred at 23 °C for 16 h. The organic phase is washed with 1 M aqueous HCl, saturated aqueous sodium chloride, is dried over magnesium sulfate, and concentrated *in vacuo*. Trituration with methylene chloride-ether affords 7.2 g of (2*S*,3*S*)-2-tert-butoxycarbonylamino-3-methylpentanoic acid 1,3-thiazol-2-ylamide as a solid.

APCI-MS *m/z* 314.3 (*M*+*H*)⁺.

15

Example 83b; (2*S*,3*S*)-2-Amino-3-methylpentanoic Acid 1,3-Thiazol-2-ylamide Hydrochloride

A solution of 7.2 g (23.0 mmol) of (2*S*,3*S*)-2-tert-butoxycarbonylamino-3-methylpentanoic acid 1,3-thiazol-2-ylamide in 30 mL of dichloromethane is treated at 25 °C with 10 mL of 4 M hydrogen chloride in dioxane. After 8 h at 25 °C the mixture is concentrated *in vacuo* and the residue is filtered and dried *in vacuo* to afford 5.7 g (100%) of (2*S*,3*S*)-2-amino-3-methylpentanoic acid 1,3-thiazol-2-ylamide hydrochloride as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 7.67 (d, 1H), 7.41 (d, 1H), 4.30 (d, 1H), 2.21 (m, 1H), 1.59 (m, 1H), 1.26 (m, 1H), 1.13 (d, 3H), 0.98 (t, 3H) ppm.

ESI-MS *m/z* 214 (*M*+*H*)⁺, 212 (*M*-*H*)⁻.

(2*S*,3*S*)-2-Amino-3-methylpentanoic acid 1,3-thiazol-2-ylamide hydrochloride (500 mg, 2.0 mmol) is shaken in 10 mL dichloromethane with 3 mL of 10% aqueous sodium carbonate. Separation and concentration of the organic phase affords 382 mg of (2*S*,3*S*)-2-amino-3-methylpentanoic acid 1,3-thiazol-2-ylamide as an oil which is used without further purification.

30

Example 83c; (2R,3S)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1S,2S)-2-Methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide

5 (2R,3S)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid (200 mg, 0.541 mmol) in 25 mL of DMF is treated with 78 mg (0.596 mmoles) of HOBt, 0.6 g (5.96 mmole) of triethylamine, and 264 mg (0.596 mmoles) of BOP. After 15 min at 0-5 °C 127 mg (0.596 mmoles) of (2S,3S)-2-amino-3-methylpentanoic acid 1,3-thiazol-2-ylamide is added. The reaction stirred at
10 25 °C for 17 h and is then concentrated to dryness. The resulting oil is partitioned between EtOAc and saturated sodium bicarbonate. The organics are dried over magnesium sulfate, concentrated and chromatographed on silica gel (elution with 50% EtOAc - hexanes) to give 131 mg of (2R,3S)-3-(formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid
15 [(1S,2S)-2-methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide as an oil. ESI-MS m/z 567 (M+H)⁺.

Example 83; (2R,3S)-3-(Formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic Acid [(1S,2S)-2-Methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide
20

(2R,3S)-3-(Formyl-2-tetrahydropyranyloxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid [(1S,2S)-2-methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide (131 mg, 0.23 mmol) in 20 mL of 80% acetic acid is allowed to stir at 40
25 °C for 17 h and is concentrated to dryness. The resulting solid is treated with toluene and concentrated *in vacuo*. Treatment of the residue with ether and collection of the resulting solid affords 75 mg of (2R,3S)-3-(formyl-hydroxyamino)-2-(2-methyl-1-propyl)-6,6,6-trifluorohexanoic acid [(1S,2S)-2-methyl-1-(1,3-thiazol-2-ylcarbamoyl)-1-butyl]amide.
30 ¹H NMR (400 MHz, d₆-acetone) δ 9.10 (s, 1H), 8.5 (s, 1H), 8.10 (s, 1H), 7.92-7.80 (d, 1H), 7.42 (d, 1H), 7.17 (d, 1H), 4.90-5.00 (m, 1H), 4.45 (m, 1H), 3.35 (s, 3H), 3.20-3.00 (m, 1H), 2.25-2.00 (m, 3H), 1.90-1.50 (m, 3H), 1.30-1.10 (m, 4H), 0.95 (d, 3H), 0.80 (d, 3H) ppm.
ESI-MS m/z 483 (M+H)⁺.

35

PHARMACOLOGY

The efficacy of compounds of the present invention as inhibitors of matrix metalloproteases, TNF α converting enzyme and TNF α cellular release can be evaluated and measured using pharmacological methods known in the art or as described in detail below based on similarly established methodologies.

Pharmacological Example 1

10 A. Matrix Metalloprotease Inhibition Protocol

The potency of compounds of the invention as inhibitors of 19 kD truncated collagenase-1 (MMP-1), 20 kD truncated collagenase-3 (MMP-13), stromelysin-1 (MMP-3), and 50 kD truncated gelatinase B (MMP-9) is determined according to the general procedure of Bickett et. al. (*Anal. Biochem.* 1993, 212, 58-64) using the fluorogenic substrate, DNP-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂ (DNP = 15 2,4-dinitrophenyl, NMA = N-methylantranilic acid). Assays are conducted in a total volume of 0.180 mL assay buffer (200 mM NaCl, 50 mM Tris, 5 mM CaCl₂, 10 μ M ZnSO₄, 0.005% Brij 35, pH 7.6) in each well of a black 96 - well microtiter plate. 19 kD collagenase-1, 20 kD collagenase-3, stromelysin-1, and 50 kD gelatinase B concentrations are adjusted to 500 pM, 30 pM, 5 nM, and 100 pM, respectively. A dose response is generated using an eleven - point, 3 - fold serial dilution with initial starting test compound concentrations of 100, 10, or 1 μ M. Inhibitor and enzyme reactions are incubated for 30 minutes at ambient temperature and then initiated with 10 μ M fluorogenic substrate (above). The product formation is measured at 25 Excitation₃₄₃/Emission₄₅₀ nm after 45-180 minutes using a Fluostar SLT fluorescence analyzer. Percent inhibition is calculated at each inhibitor concentration and the data are plotted using standard curve fitting programs. IC₅₀ values are determined from these curves. Assays are run at low substrate concentration ([S]<<K_m) such that the calculated IC₅₀ values are equivalent to K_i within 30 experimental error.

B. TNF α Converting Enzyme Inhibition Protocol

The potency of compounds of the invention as inhibitors of cell - free tumor necrosis factor α converting enzyme is determined as follows; Membrane preparation 35 from MonoMac 6 cells (subfractionated extract from equivalent of 6x10⁶ cells per 60 μ l assay) is incubated for 1 hr with 200 nM radiolabeled substrate (Biotin-SPLAQAVRSSSRT-(³H)P-S-NH₂, 4.1 Ci/mmol, ref # 0935 from Zeneca) in 10 mM

hepes buffer, 250 mM sucrose, pH 7.5. The reaction is quenched by addition of streptavidin SPA beads (Amersham RPNQ0006), with excess binding capacity relative to substrate, suspended in 250 mM EDTA, pH 8.0. Binding is complete within 15 minutes and plates are counted in a Wallac 1450 Microbeta liquid scintillation counter. Percent inhibition is calculated at each inhibitor concentration and the data are plotted using standard curve fitting programs. IC_{50} values are determined from these curves. Assays are run at low substrate concentration ($[S] \ll K_m$) such that the calculated IC_{50} values are equivalent to K_i within experimental error.

C. Cell - Based $TNF\alpha$ Release Inhibition Protocol

The potency of compounds of the invention as inhibitors of release of soluble tumor necrosis factor α from stimulated monocytes in vitro is determined as follows; LPS/PMA solution for assay consisting of a) 4 μ L of 5 mg/mL LPS stock and b) 6 μ L of 10 mg/mL PMA stock are added to 500 μ L of medium (RPMI + 10% FBS + penicillin/streptomycin + l-glutamine). This solution is then diluted 1:1000 (40 ng/mL and 120 ng/mL) for use later in the assay. Compounds (10 mM) are serially diluted 1:3 in DMSO. Compound dilutions (20 μ L) are added to a sterile round bottom 96 well plate (20 μ L:200 μ L total volume = 1:10 for final concentrations of 50 μ M for test compounds). MonoMac 6 cell suspension (130 μ L, 1.5×10^6 cells/mL) is then added to each well resulting in 2×10^5 cells/well. LPS/PMA (50 μ L) solution is then added to each well (final concentrations of 10 ng/mL and 30 ng/mL respectively). The plate is incubated at 37 °C for 2 h then spun at 1,500 rpm for 3 min to pellet cells. The supernatant (120 μ L/well) is removed to a new round bottom 96 well plate and diluted 1:10 in PBS. Then, 20 μ L of the supernatant is transferred to a Cistron $TNF\alpha$ ELISA plate and processed according to the manufacturer's instructions to quantitate levels of $TNF\alpha$. Percent inhibition of $TNF\alpha$ release is calculated at each inhibitor concentration and the data are plotted using standard curve fitting programs. IC_{50} values are determined from these curves.

Results are listed in Table 3.

Table 3

Example	TNF α Converting Enzyme K _i	Collagenase-1 K _i	Collagenase-3 K _i	Gelatinase B K _i	Stromelysin-1 K _i	TNF α Release Inhibition IC ₅₀
Example 1	+	+	+	+	+	+
Example 2	+	++	+	+	+	+
Example 3	+	+	+	+	+	+
Example 4	+	+	+	+	+	+
Example 5	+	++	+	+	++	+
Example 6	+	++	+	++	++	++
Example 7	+	+++	+++	+++	+++	+
Example 8	+	+++	+	+++	++	+
Example 9	+	+	+	+	++	++
Example 10	+	++	+	++	++	++
Example 35	+	+	+	+	++	++
Example 76	+	+	+	+	+	++
Example 77	+	+	+	+	+	+
Example 78	+	+	+	+	+	++
Example 79	+	+	+	+	+	+
Example 80	+	++	+	+	+	++++
Example 81	+	+	+	+	++	+++
Example 82	+	+	+	+	++	++
Example 83	+	+	+	+	+	++

Key: + <100nM
 ++ 100nM - 500nM
 +++ 500 nM - 1 μ M
 ++++ > 1 μ M

Pharmacological Example 2

10 Murine LPS - Stimulated Serum TNF Inhibition Protocol

The potency of compounds of the invention as inhibitors of serum TNF α elevation in mice treated with lipopolysaccharide (LPS) is determined as follows;

- a) for subcutaneous (s.c.) administration, test compound is dissolved in DMSO and added to a mixture of 0.9% sodium chloride solution and 30% Trappsol HPB-20 (Cyclodextrin Technology Development Inc., Gainesville, Florida USA) for a final DMSO concentration of 1%. The dosing solution is sonicated briefly and 0.2 mL is injected subcutaneously 10 min prior to LPS injection, b) for per oral (p.o.) administration, test compounds are formulated in 0.2 mL of PBS and 0.1% Tween 80 and given orally via gavage 10 min prior to LPS administration.

- 20 C3/hen female mice are injected intraperitoneally with 200 μ g/kg LPS (Escherichia coli, Serotype 0111:B4, Sigma Chemical Co, St. Louis, MO) in PBS and sacrificed 90 min later by CO₂ asphyxiation. Blood is immediately taken from the

caudal vena cava and plasma prepared and frozen at -80 °C. Plasma concentrations of TNF are measured by ELISA (Genzyme Co., Cambridge MA).

Results are listed in Table 4.

5 Table 4

Compound	Route of Administration	Dose	Percentage Inhibition of Serum TNF α
Example 2	p.o.	40 mg/kg	++
Example 9	s.c.	40 mg/kg	+++
Example 9	p.o.	80 mg/kg	++
Example 10	p.o.	40 mg/kg	+
Example 35	p.o.	40 mg/kg	++
Example 76	p.o.	40 mg/kg	+++
Example 77	p.o.	40 mg/kg	++
Example 78	p.o.	40 mg/kg	++
Example 79	p.o.	40 mg/kg	+
Example 80	p.o.	40 mg/kg	++
Example 81	p.o.	40 mg/kg	++
Example 82	p.o.	40 mg/kg	++
Example 83	p.o.	40 mg/kg	++

Key: + 25% - 50%

++ 50% - 75%

+++ >75%

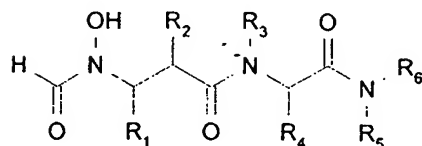
10

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for inflammatory conditions, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

25

Claims

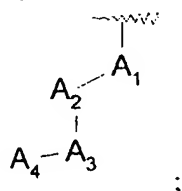
1. A compound of the formula (II)



5

(II)

where R₁ is



where A₁ is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, or a direct bond;

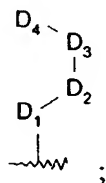
10 A₂ is C(O)NR₇, NR₇C(O), SO₂NR₇, NR₇SO₂, NR₇, S, SO, SO₂, O, C(O), C(O)O, OC(O), or a direct bond, where R₇ is as defined below;

A₃ is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, or a direct bond;

A₄ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heteroaryl, aryl,

15 NR₈R₉, OR₈, or hydrogen, where R₈ and R₉ are as defined below;

R₂ is



20 where D₁ is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, NR₁₀(O)C, NR₁₀, S, SO, SO₂, O, O(O)C, or a direct bond, where R₁₀ is as defined below;

D₂ is S, SO, SO₂, O, C(O), C(O)O, OC(O), C(O)NR₁₁, NR₁₁C(O), NR₁₁, or a direct bond, where R₁₁ is as defined below;

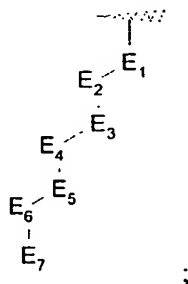
25 D₃ is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, heterocyclylene, S, SO, SO₂, O, C(O), C(O)O, OC(O), C(O)NR₁₂, NR₁₂C(O), SO₂NR₁₂, NR₁₂SO₂, NR₁₂, or a direct bond, where R₁₂ is as defined below;

D_4 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, OR_{13} , or hydrogen, where R_{13} is as defined below;

R_3 is hydrogen or lower alkyl;

5

R_4 is



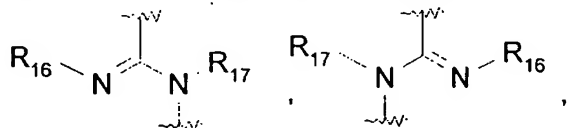
where E_1 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, $C(O)NR_{14}$, $NR_{14}C(O)$, $C(O)$, $C(O)O$, $OC(O)$, or a direct bond, where R_{14} is as defined below;

10

E_2 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{15} , S , SO , SO_2 , O , $C(O)$, $C(O)O$, $OC(O)$, or a direct bond, where R_{15} is as defined below;

15

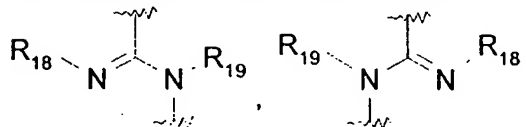
E_3 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{16} , S , SO , SO_2 , O , $C(O)$, $C(O)O$, $OC(O)$,



or a direct bond, where R_{16} and R_{17} are as defined below;

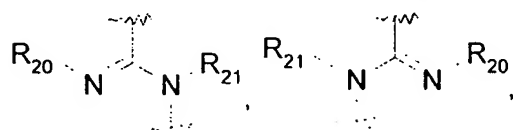
E_4 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{18} , S , SO , SO_2 , O , $C(O)$, $C(O)O$, $OC(O)$,

20



or a direct bond, where R_{18} and R_{19} are as defined below;

E_5 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{20} , S , SO , SO_2 , O , $C(O)$, $C(O)O$, $OC(O)$,



25

or a direct bond, where R_{20} and R_{21} are as defined below;

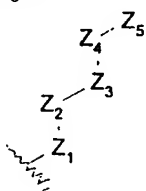
E_6 is alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, NR_{22} , S, SO, SO_2 , O, C(O), C(O)O, OC(O), or a direct bond, where R_{22} is as defined below;

- 5 E_7 is hydrogen, $NR_{23}R_{24}$, OR_{23} , SR_{23} , SOR_{23} , SO_2R_{23} , alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl, where R_{23} and R_{24} are as defined below;

R_5 is hydrogen or lower alkyl;

10

R_6 is



where Z_1 is heteroarylene;

- 15 Z_2 is lower alkylene, lower alkenylene, lower alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, C(O) NR_{25} , NR_{25} C(O), SO_2NR_{25} , $NR_{25}SO_2$, NR_{25} , S, SO, SO_2 , O, C(O), C(O)O, OC(O), or a direct bond, where R_{25} is as defined below;

- 20 Z_3 is lower alkylene, lower alkenylene, lower alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, C(O) NR_{26} , NR_{26} C(O), SO_2NR_{26} , $NR_{26}SO_2$, NR_{26} , S, SO, SO_2 , O, C(O), C(O)O, OC(O), or a direct bond, where R_{26} is as defined below;

- 25 Z_4 is lower alkylene, lower alkenylene, lower alkynylene, cycloalkylene, cycloalkenylene, arylene, heterocyclylene, heteroarylene, C(O) NR_{27} , NR_{27} C(O), SO_2NR_{27} , $NR_{27}SO_2$, NR_{27} , S, SO, SO_2 , O, C(O), C(O)O, OC(O), or a direct bond, where R_{27} is as defined below;

Z_5 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heteroaryl, aryl, $NR_{28}R_{29}$, OR_{28} , or hydrogen, where R_{28} and R_{29} are as defined below;

- 30 R_7 , R_8 , R_9 , R_{14} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , R_{28} , and R_{29} are, independently, hydrogen, alkyl, alkynyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, or heteroaryl;

R_{10} , R_{11} , R_{12} , and R_{13} are, independently, hydrogen, alkyl, alkynyl, alkenyl, cycloalkyl, cycloalkenyl, or heterocyclyl;

and a pharmaceutically acceptable salt, solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug thereof.

- 5 2. A compound as claimed in claim 1 wherein
R₁ is methyl, ethyl, isopropyl, n-propyl or 3,3,3-trifluoro-n-propyl;
R₂ is isobutyl or sec-butyl;
R₃ is hydrogen;
R₄ is tert-butyl, sec-butyl, 1-methoxy-1-ethyl or 2-(2-pyridylcarbonylamino)-1-ethyl;
10 R₅ is hydrogen; and
R₆ is 2-thiazolyl or 2-pyridyl.
3. A compound as claimed in claim 1 or claim 2 selected from the compound of
Example 35; or a pharmaceutically acceptable salt, solvate, biohydrolyzable ester,
15 biohydrolyzable amide, affinity reagent, or prodrug thereof.
4. A compound as claimed in claim 1 or claim 2 selected from the compounds of
Examples 76, 77, 78, 79, 80, 81, 82 or 83; or a pharmaceutically acceptable salt,
solvate, biohydrolyzable ester, biohydrolyzable amide, affinity reagent, or prodrug
20 thereof.
5. A compound of formula (II) as claimed in any one of claims 1 to 4 for use in
therapy.
- 25 6. A pharmaceutical composition comprising a pharmaceutically acceptable
carrier and a pharmacologically effective amount of a compound as claimed in any
one of claims 1 to 4.
7. Use of a compound as claimed in any one of claims 1 to 4 in the preparation of
30 a medicament for inhibiting the cellular release of tumour necrosis factor alpha.
8. Use of a compound as claimed in any one of claims 1 to 4 in the preparation of
a medicament for inhibiting a matrix metalloprotease.
- 35 9. Use of a compound as claimed in any one of claims 1 to 4 in the preparation of
a medicament for inhibiting the shedding of cell surface protein ectodomains.

10. Use of a compound as claimed in any one of claims 1 to 4 in the preparation of a medicament for inhibiting the growth of tumour metastases, or for the treatment of diabetes, or for the treatment of arthritis.
- 5 11. A method of inhibiting the intracellular release of tumor necrosis factor alpha in a mammalian subject which comprises administering to said subject an effective amount of a compound as claimed in any one of claims 1 to 4.
- 10 12. A method of inhibiting a matrix metalloprotease in a mammalian subject which comprises administering to said subject an effective amount of a compound as claimed in any one of claims 1 to 4.
- 15 13. A method of inhibition of shedding of cell surface protein ectodomains in a mammalian subject which comprises administering to said subject an effective amount of a compound as claimed in any one of claims 1 to 4.
- 20 14. A method of inhibiting the growth of tumour metastases, or a method for the treatment of diabetes, or a method for the treatment of arthritis, in a mammalian subject which comprises administering to said subject an effective amount of a compound as claimed in any one of claims 1 to 4.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/01015

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D277/46 A61K31/425 C07D213/75 A61K31/44 C07D285/12
C07D239/42 C07D417/12

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 03783 A (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 6 February 1997 see claims ---	1-14
Y	WO 96 16027 A (SYNTEX INC) 30 May 1996 see claims ---	1-14
Y	WO 94 10990 A (BRITISH BIO TECHNOLOGY LIMITED) 26 May 1994 see claims ---	1-14
Y	WO 95 19956 A (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 27 July 1995 see claims ---	1-14
P,X	WO 97 19053 A (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 29 May 1997 see claims -----	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 June 1998

Date of mailing of the international search report

30. 06. 98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/01015

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-14
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 11-14
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/01015

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9703783	A	06-02-1997	AU 6663396 A GB 2318353 A	18-02-1997 22-04-1998
WO 9616027	A	30-05-1996	AU 4289796 A BR 9509802 A CZ 9701565 A EP 0793643 A FI 972160 A HU 77533 A NO 972307 A PL 321024 A	17-06-1996 30-09-1997 12-11-1997 10-09-1997 22-05-1997 28-05-1998 22-07-1997 24-11-1997
WO 9410990	A	26-05-1994	AT 150300 T AU 5430194 A DE 69309094 D DE 69309094 T EP 0667770 A ES 2101358 T JP 8505605 T US 5691382 A	15-04-1997 08-06-1994 24-04-1997 31-07-1997 23-08-1995 01-07-1997 18-06-1996 25-11-1997
WO 9519956	A	27-07-1995	AT 165817 T AU 682920 B AU 1459795 A BR 9506535 A CA 2181570 A CN 1138851 A DE 19581347 T DE 69502378 D EP 0740652 A EP 0822186 A FI 962904 A GB 2299334 A,B GB 2316078 A,B HU 75059 A JP 9508361 T NO 963030 A NZ 278627 A PL 315745 A SK 94196 A	15-05-1998 23-10-1997 08-08-1995 16-09-1997 27-07-1995 25-12-1996 05-12-1996 10-06-1998 06-11-1996 04-02-1998 19-07-1996 02-10-1996 18-02-1998 28-03-1997 26-08-1997 19-09-1996 24-04-1997 25-11-1996 05-03-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/01015

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9519956 A		US 5747514 A ZA 9500480 A	05-05-1998 07-02-1996
WO 9719053 A	29-05-1997	AU 7633096 A	11-06-1997